UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

A.D. 1308 unipg UNIVERSITÀ DEGLI STUDI DI PERUGIA

CLMMC AA 2023/24

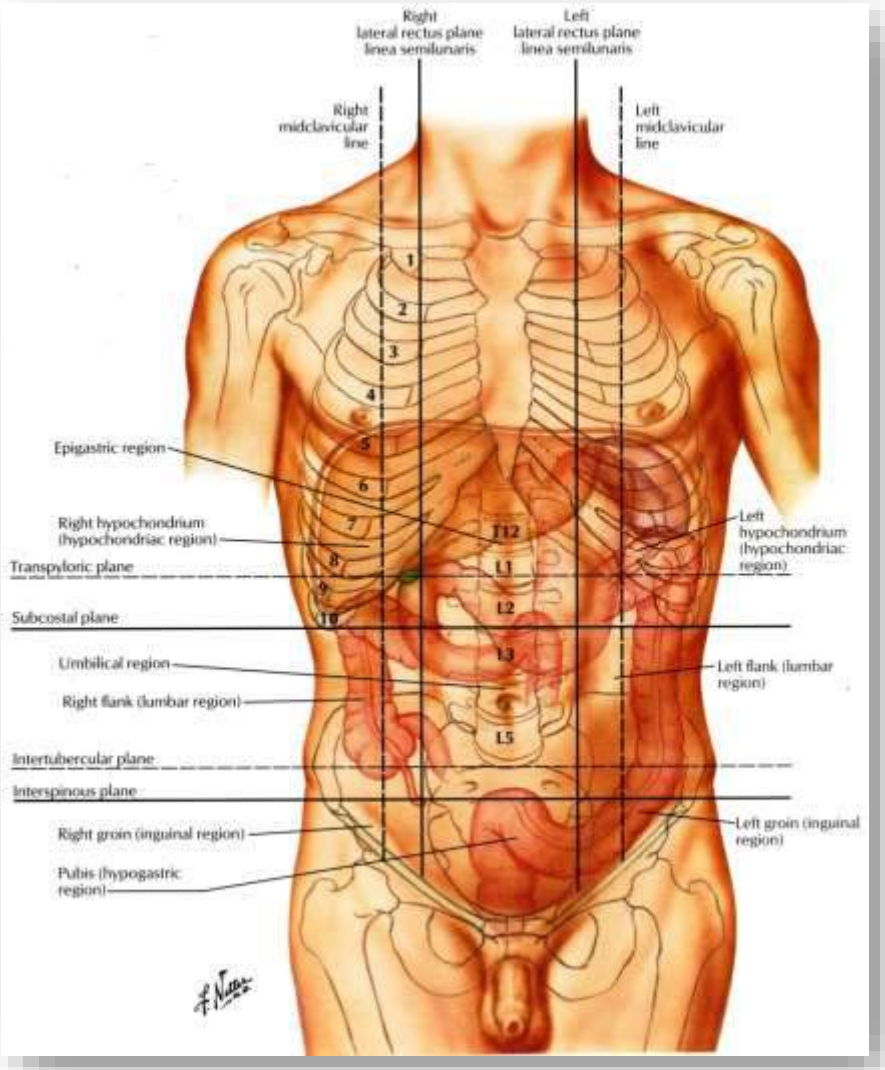
Patologia sistematica VI
Gastroenterologia

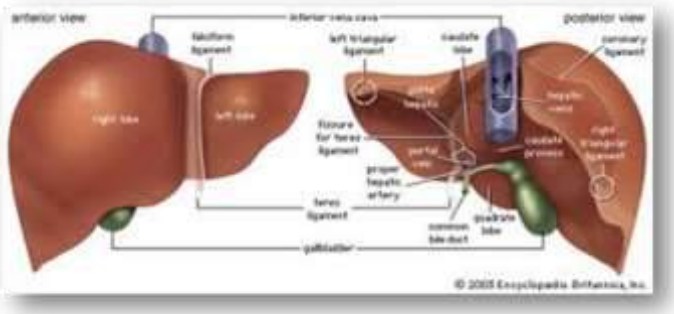
Prof. Stefano Fiorucci

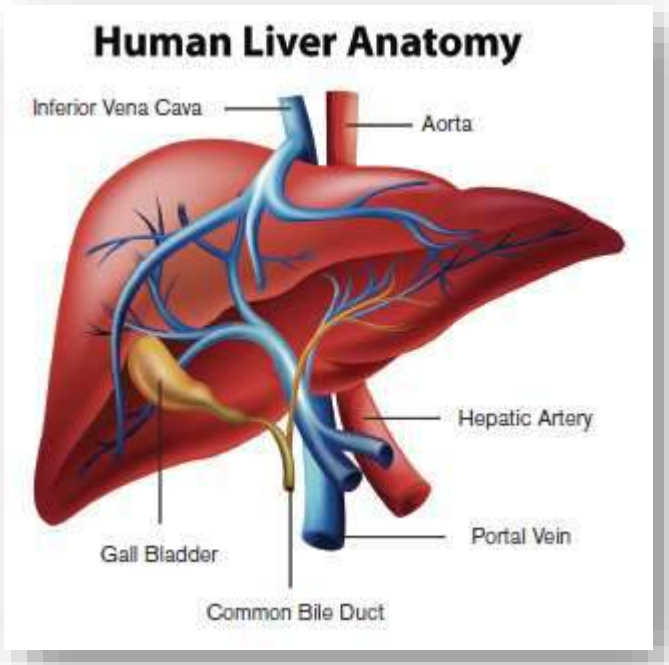
Liver clinical anatomy

Harrison's Principles of Internal Medicine – 19-20° Ed.

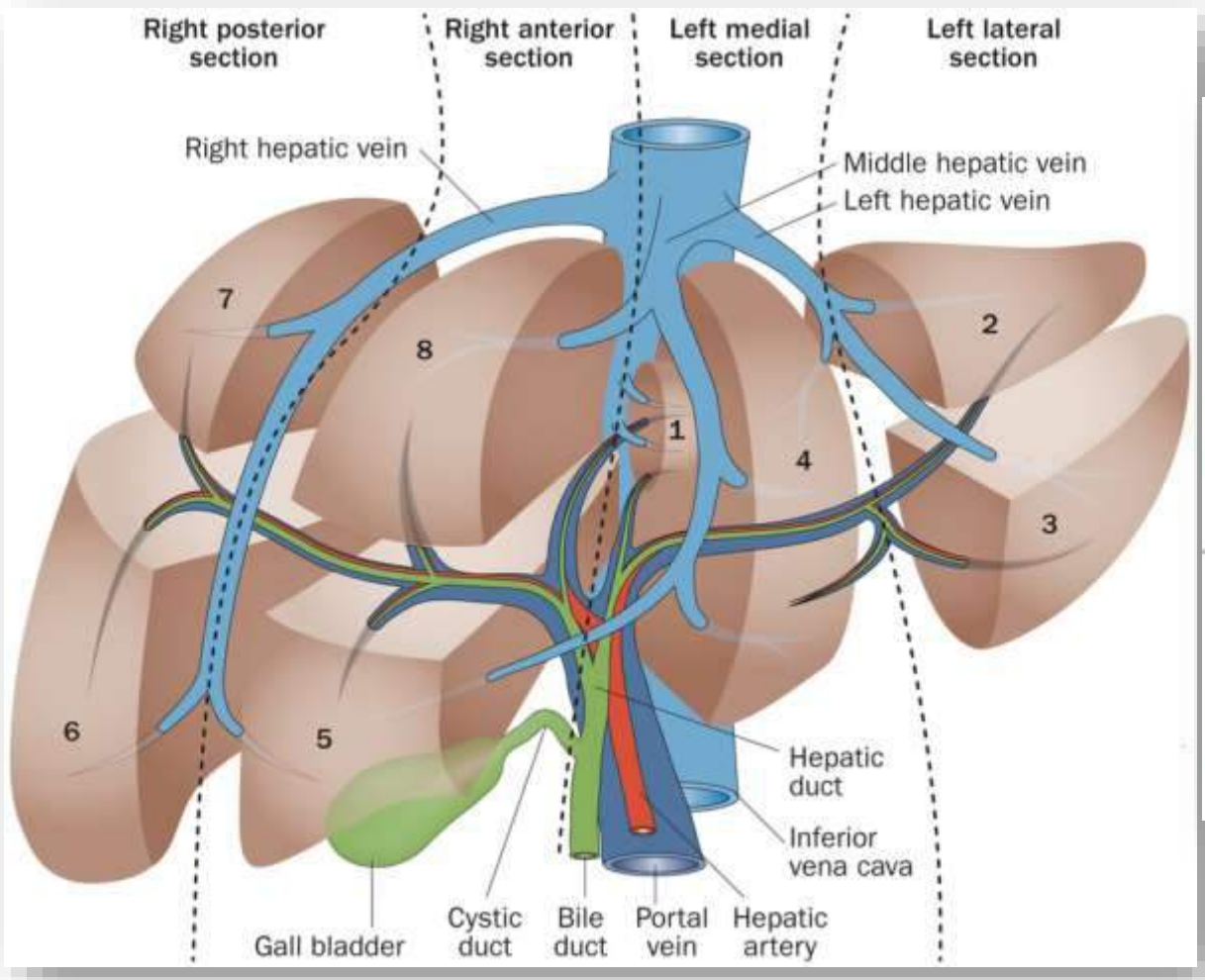
Liver

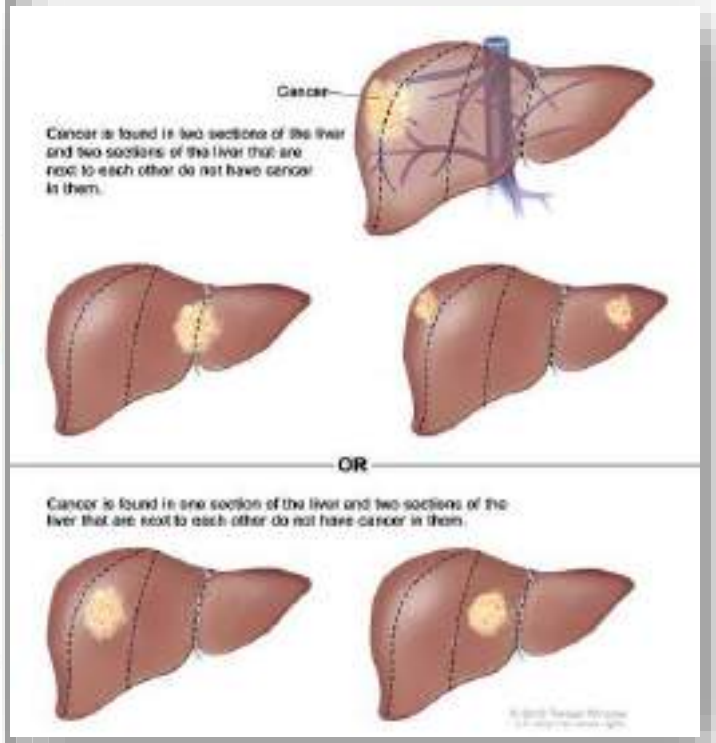

Right lateral rectus plane linea semilunaris
Left lateral rectus plane linea semilunaris
Right midclavicular line
Left midclavicular line
Epigastric region
Right hypochondrium (hypochondriac region)
Left hypochondrium (hypochondriac region)
Transpyloric plane
Subcostal plane
Umbilical region
Right flank (lumbar region)
Left flank (lumbar region)
Intertubercular plane
Interspinous plane
Right groin (inguinal region)
Left groin (inguinal region)
Pubis (hypogastric region)
1
2
3
4
5
6
7
8
9
10
T12
L1
L2
L3
L5



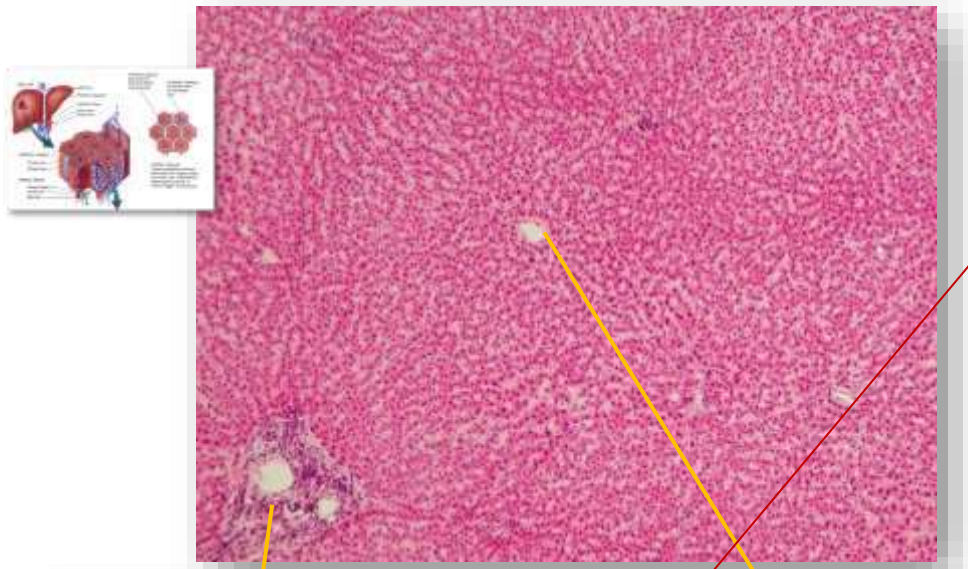

Human Liver Anatomy
Inferior Vena Cava
Aorta
Hepatic Artery
Portal Vein
Gall Bladder
Common Bile Duct

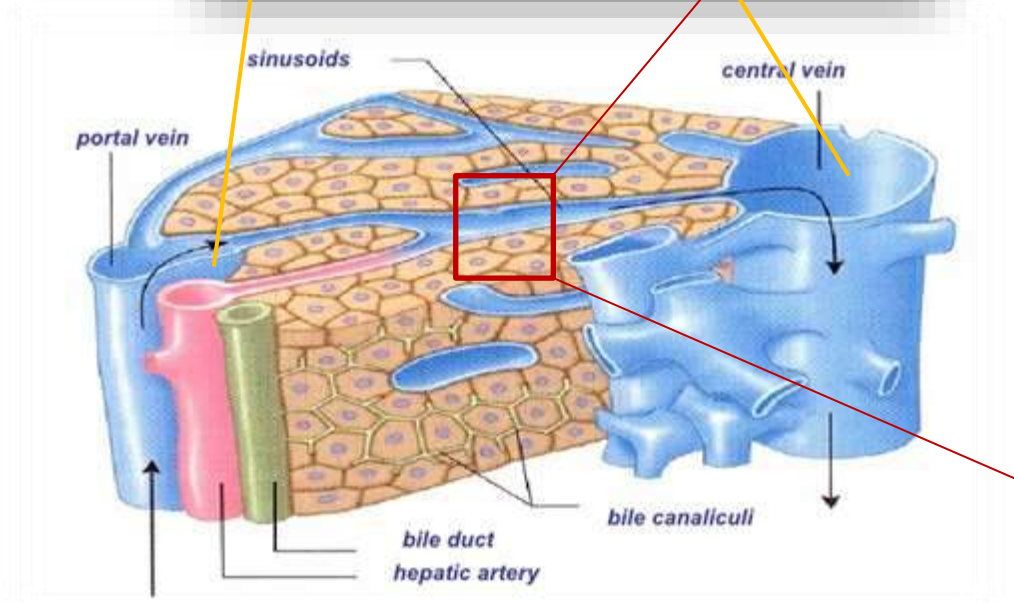
Hepatic lobules by Coinaud

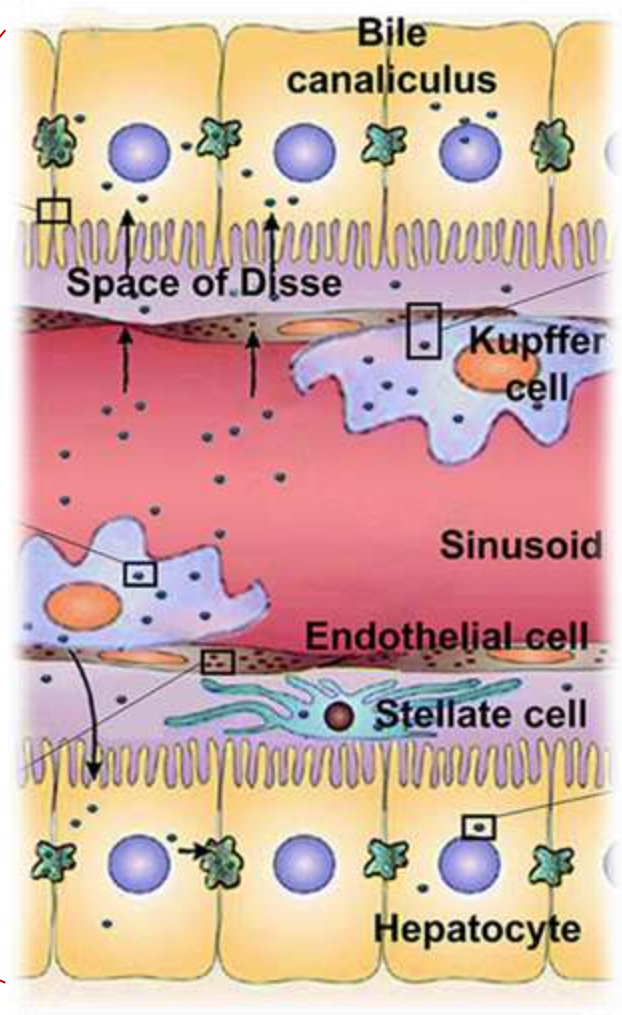




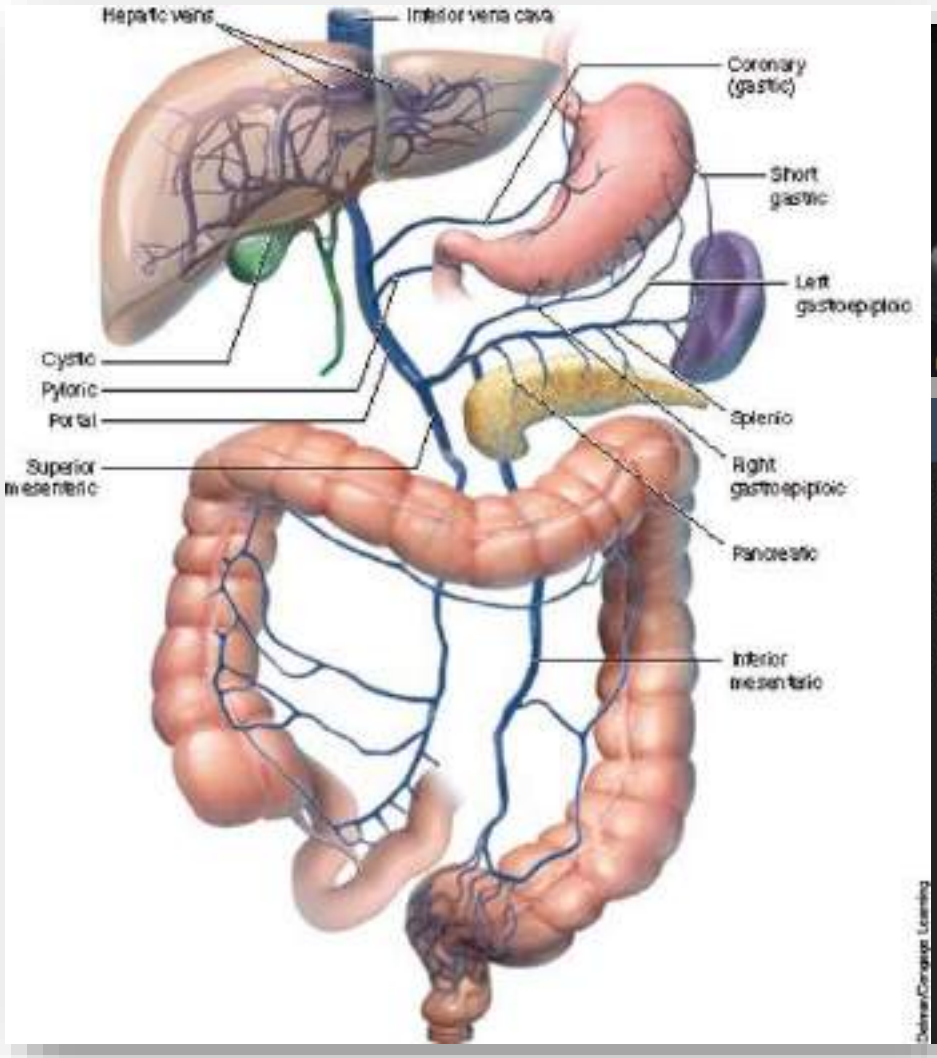
Liver functional anatomy

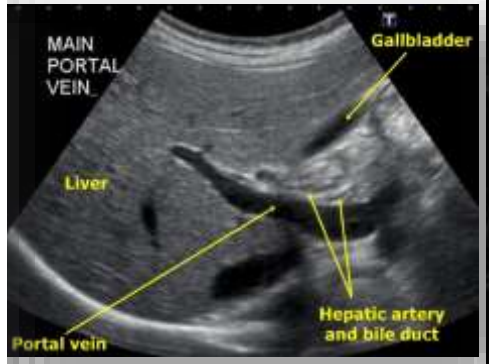


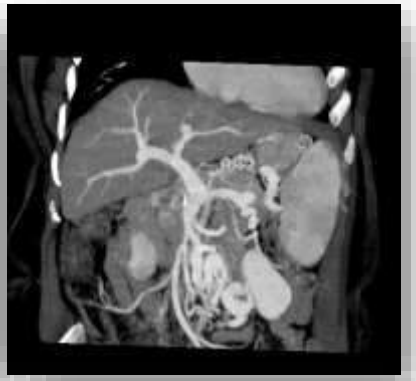


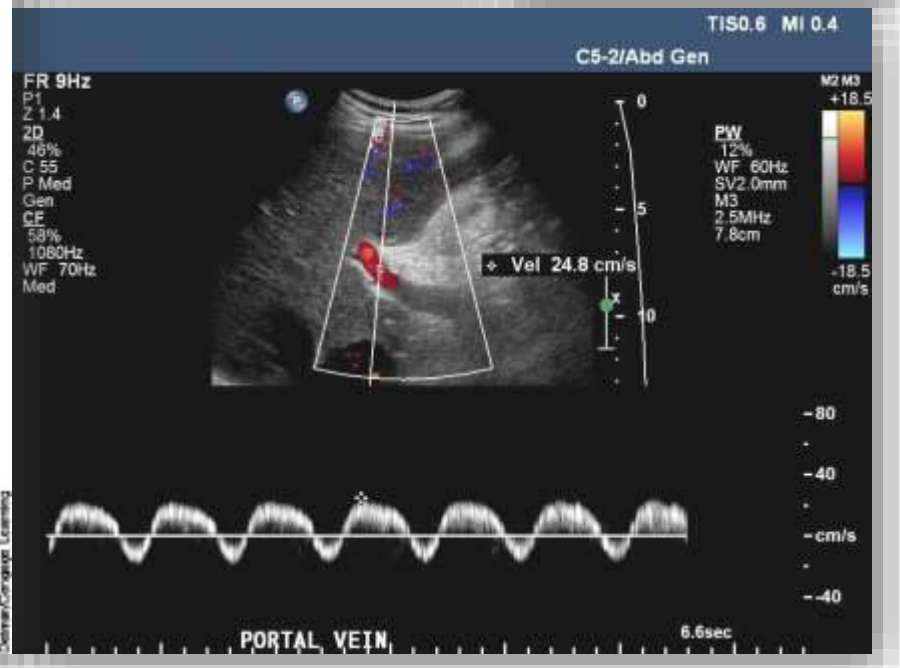


Portal vein anatomy and pathology

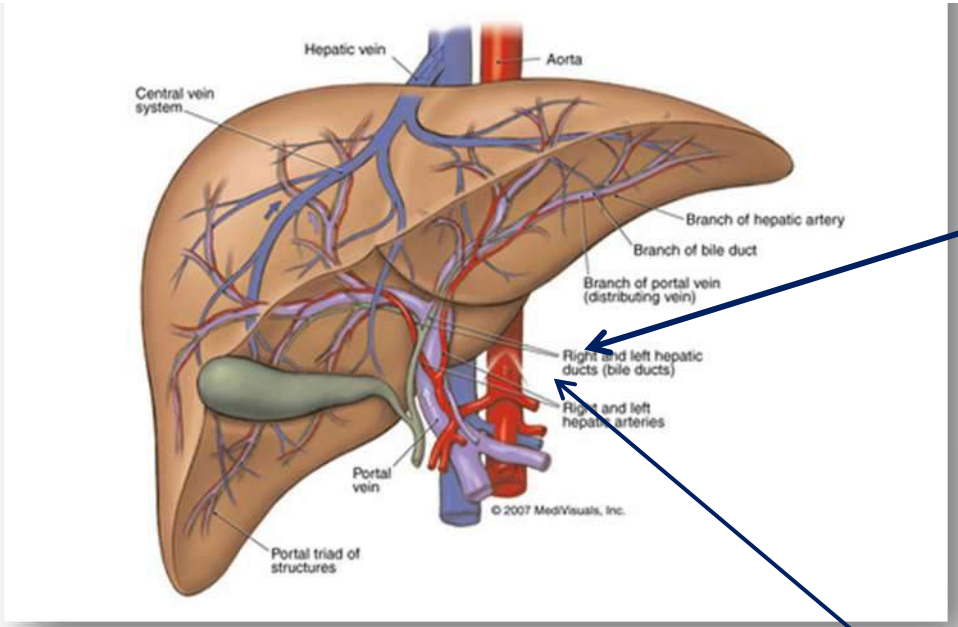


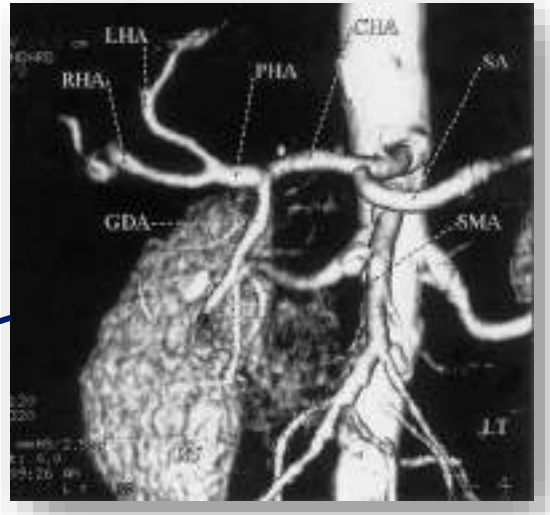


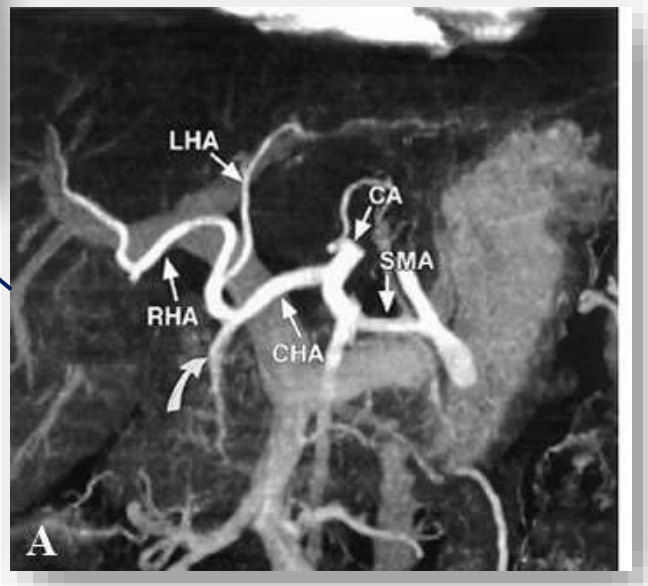




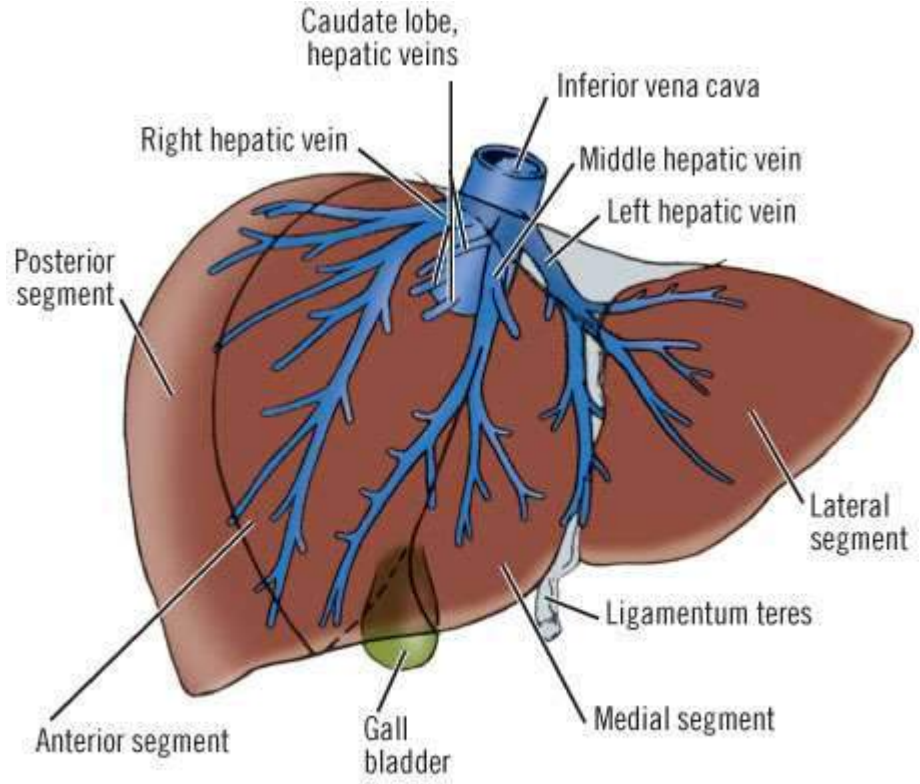
Hepatic artery

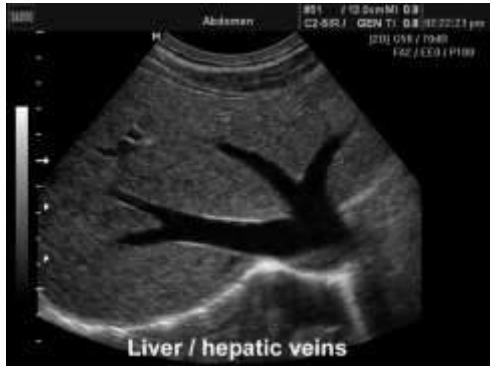


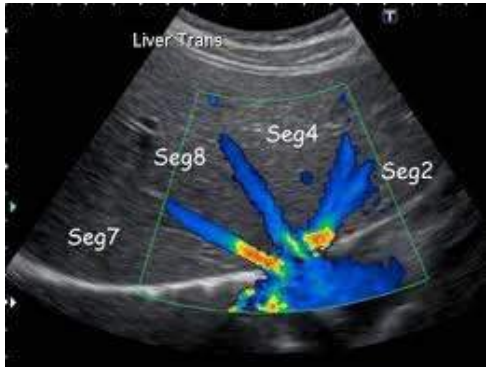


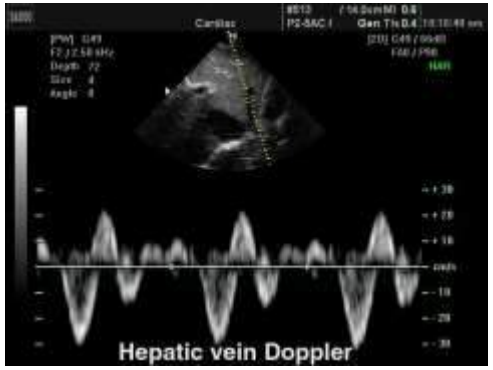


Hepatic veins

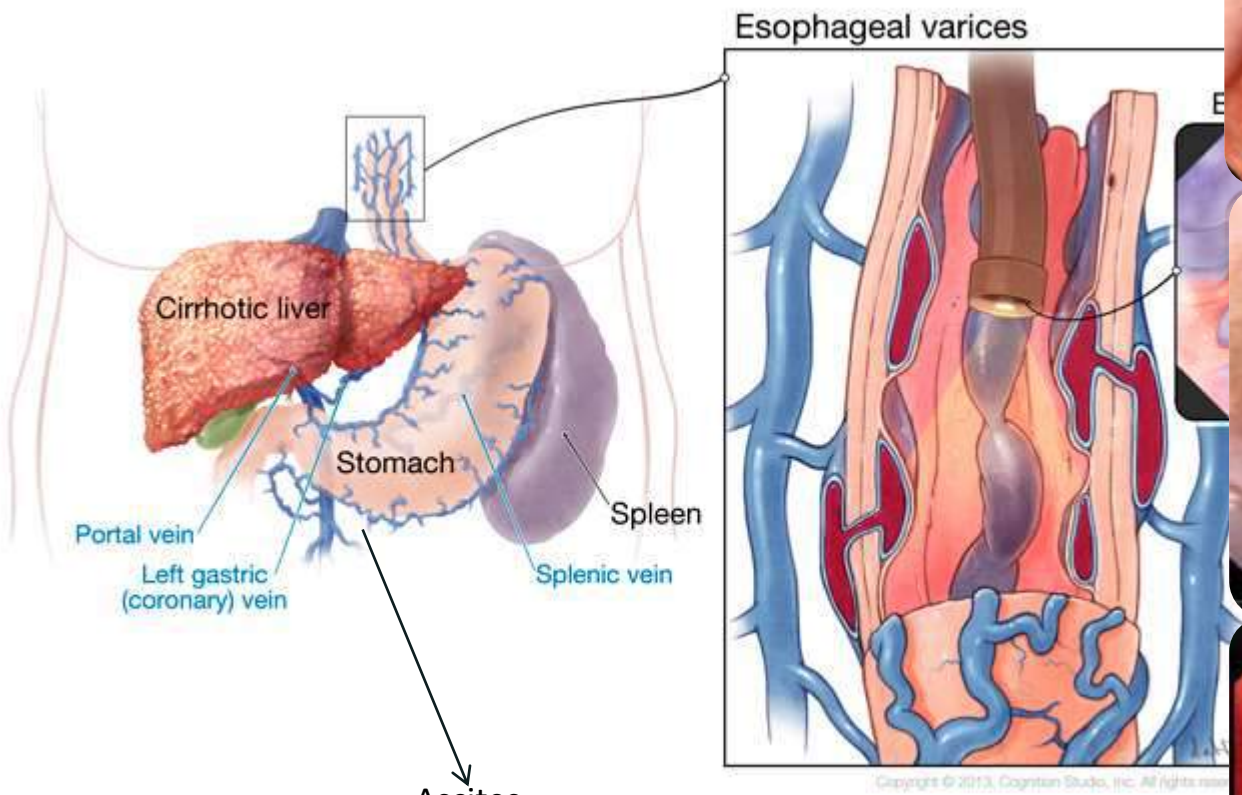


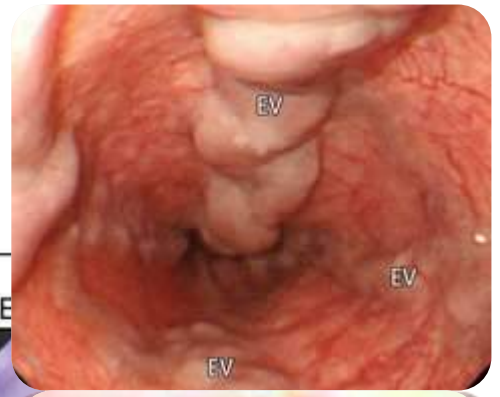


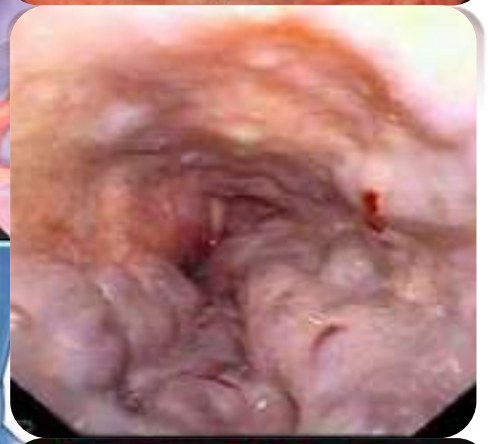


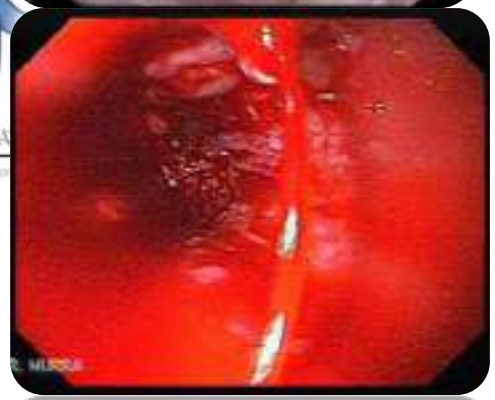


Liver cirrhosis causes portal hypertension

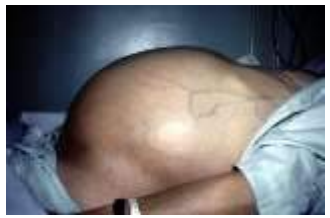




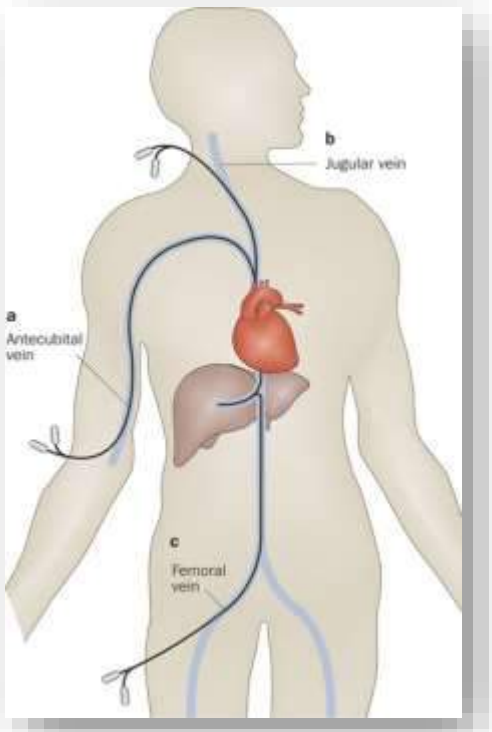


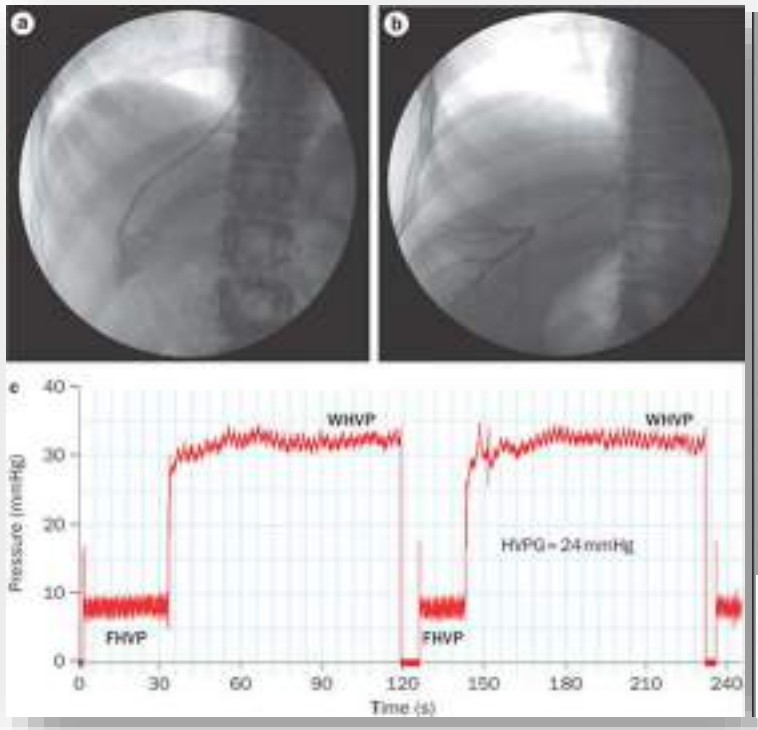


Ascites



Measurement of portal vein gradient





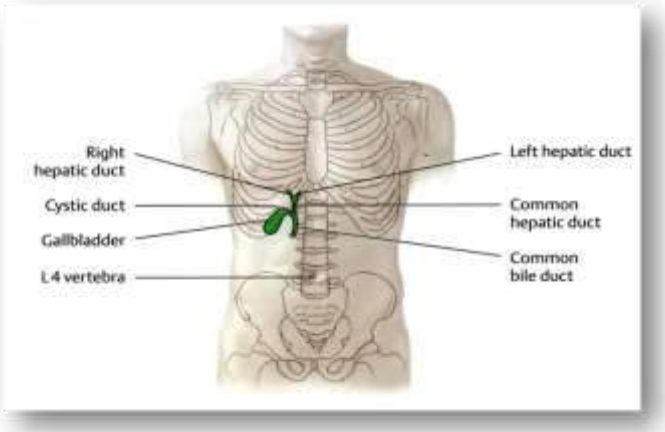
WHVP – FHVP <5 mm Hg

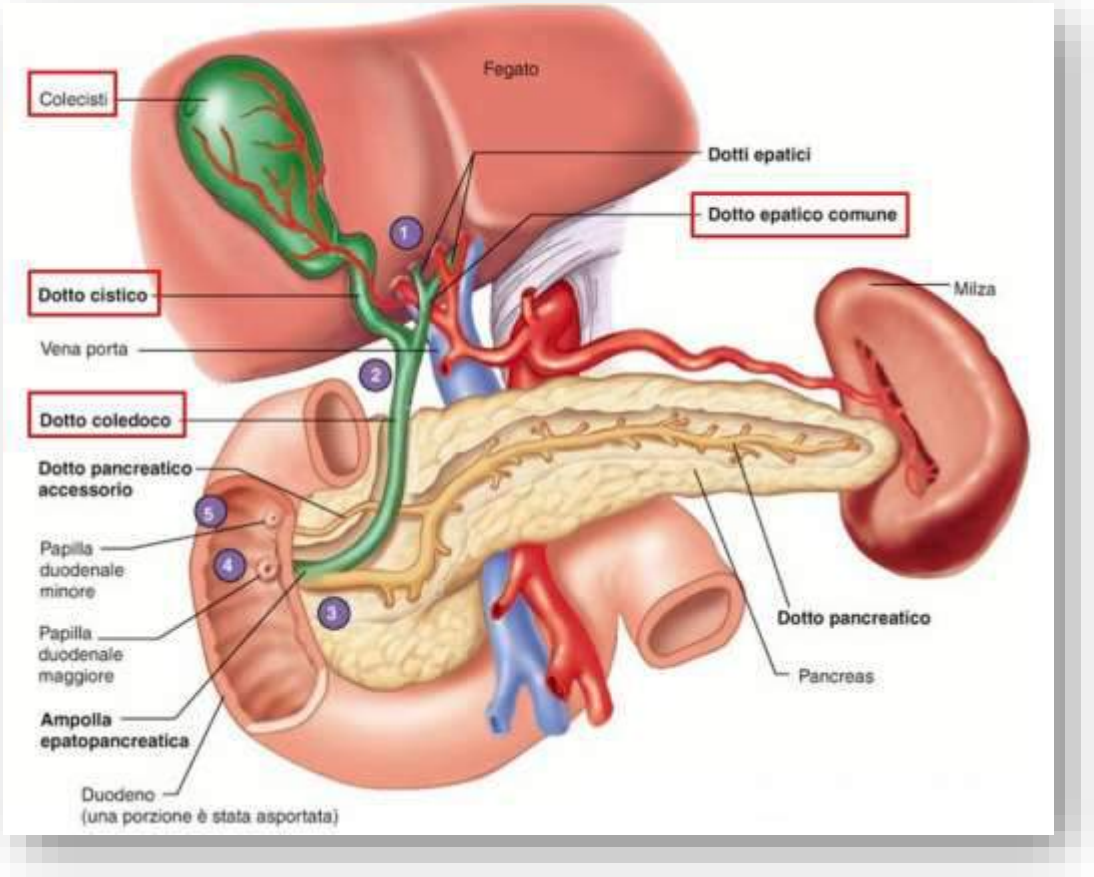
Prognostic Value of HVPG in Patients with Chronic Liver Disease	
Measurement	**Significance**
1-5 mm Hg	Normal
6-10 mm Hg	Preclinical sinusoidal portal hypertension
≥ 10 mm Hg	Clinically significant portal hypertension
≥ 12 mm Hg	Increased risk for rupture of varices
≥ 16 mm Hg	Increased risk of mortality
≥ 20 mm Hg	Treatment failure and mortality in acute variceal bleeding

TIPS

Transiugular Intra-heaptic Porto-systemic Shunt

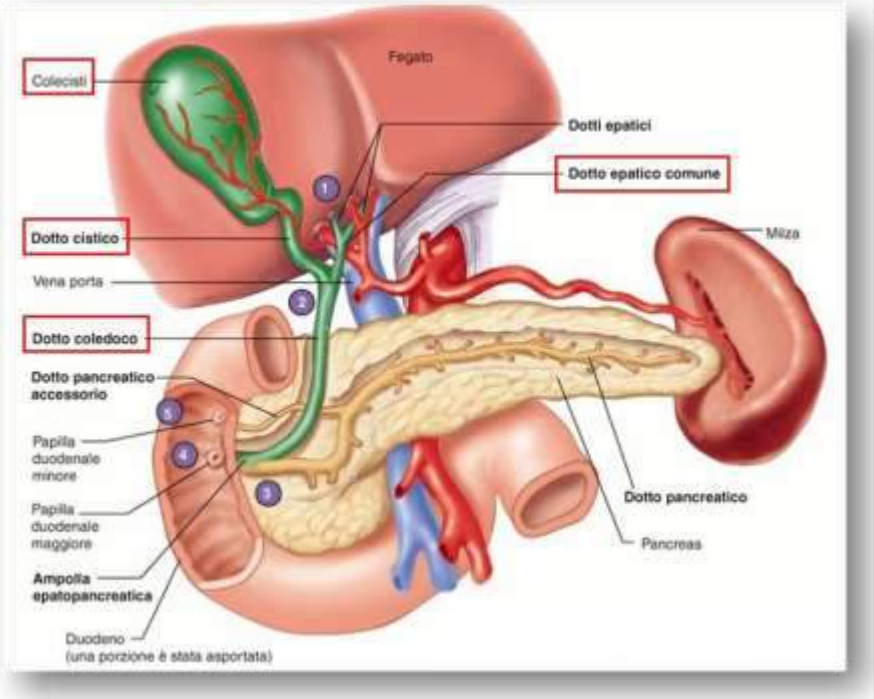
Biliary system

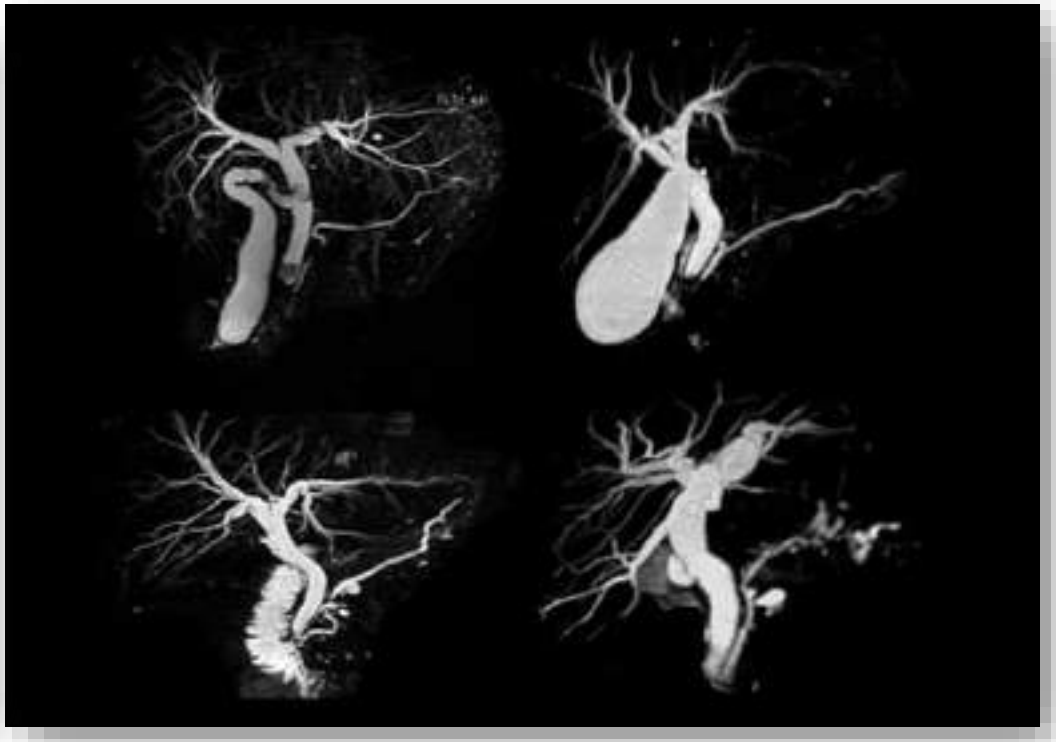




Biliary system

MR and colangio-MR



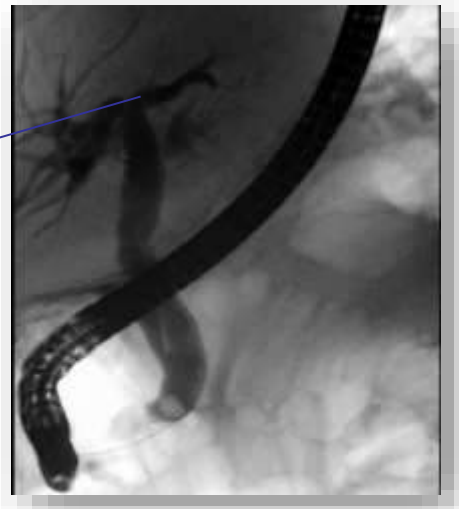


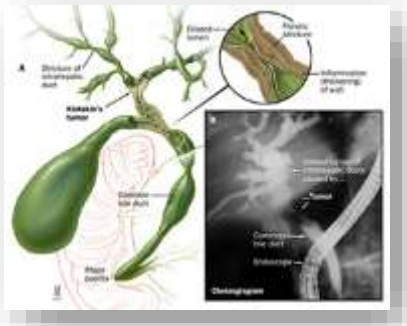
Biliary system

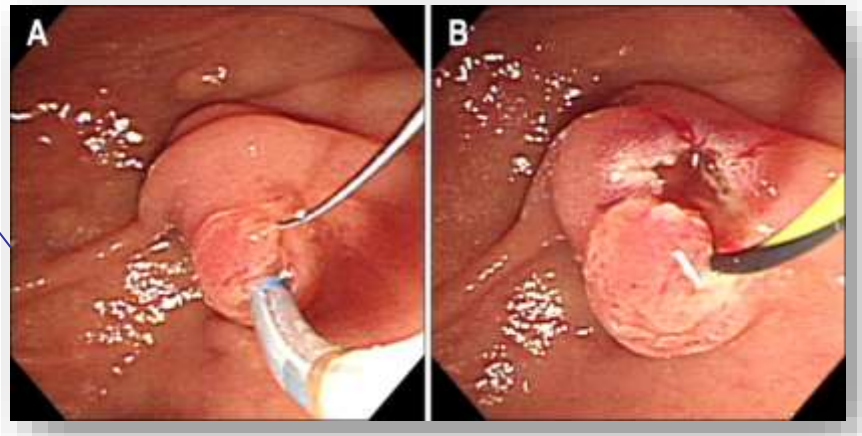
ERCP- Endoscopic retrograde cholangiography

Endoscopic sphintherotomy

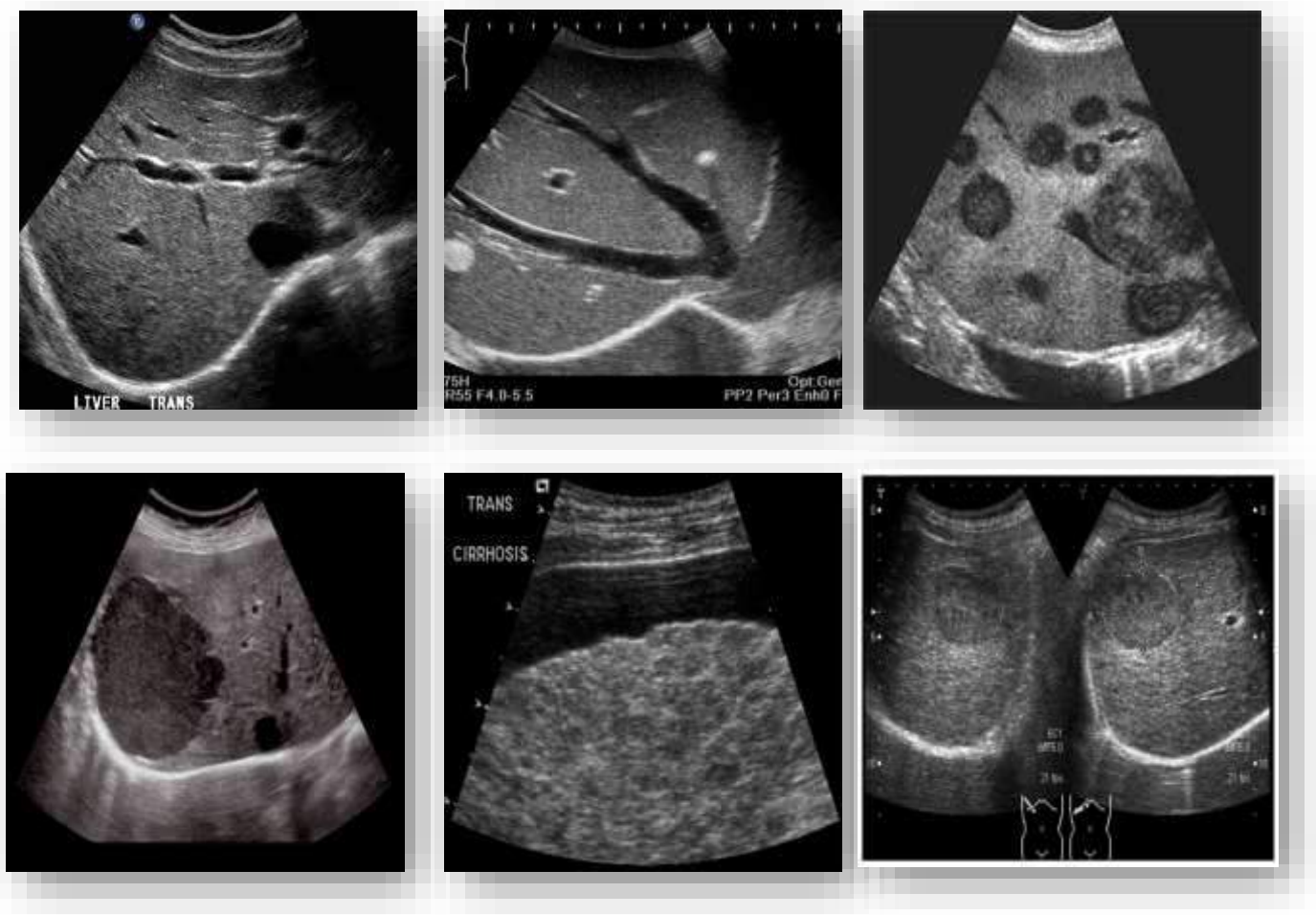
ERCP sphincterotomy and Biliary stone Extraction.mp4







Liver anatomy and pathology: sonography



Fiorucci S, Atlante di ecografia in gastroenterologia ed epatologia , 2003

Contrast enhanced US (CEUS)

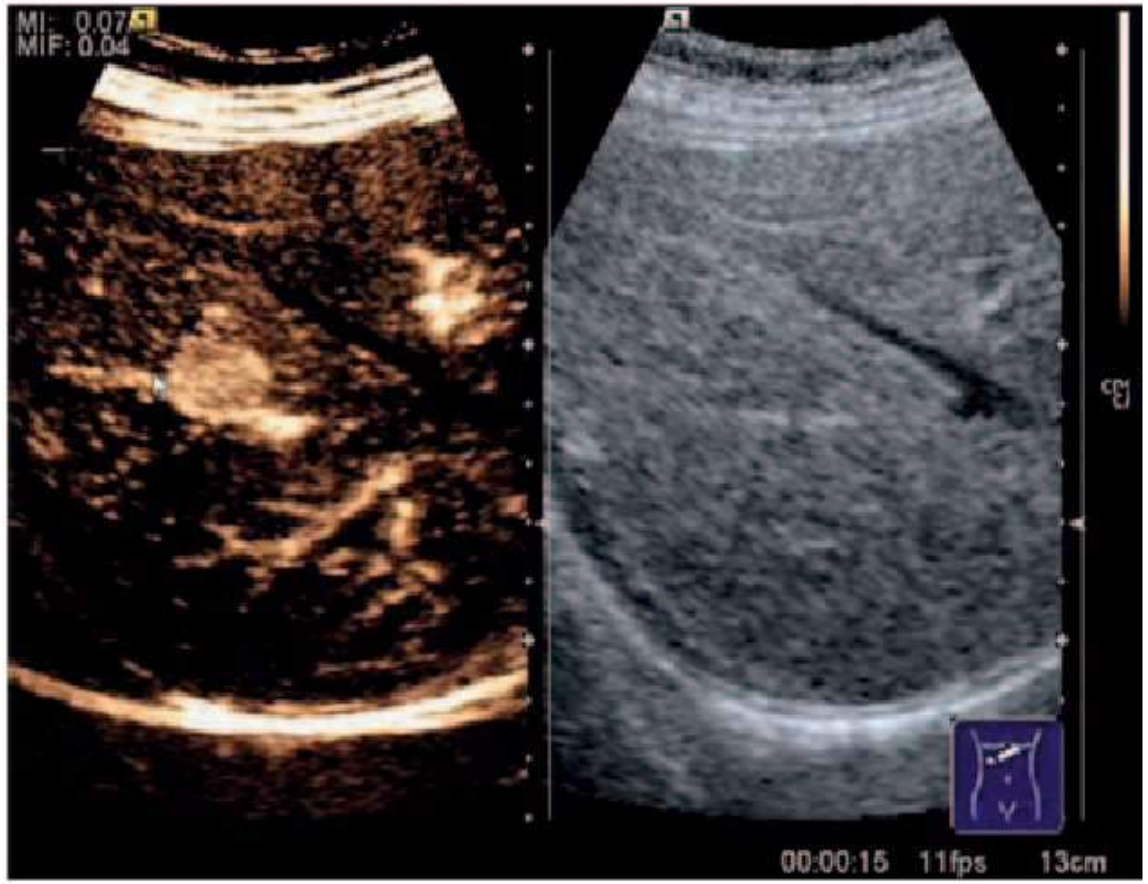
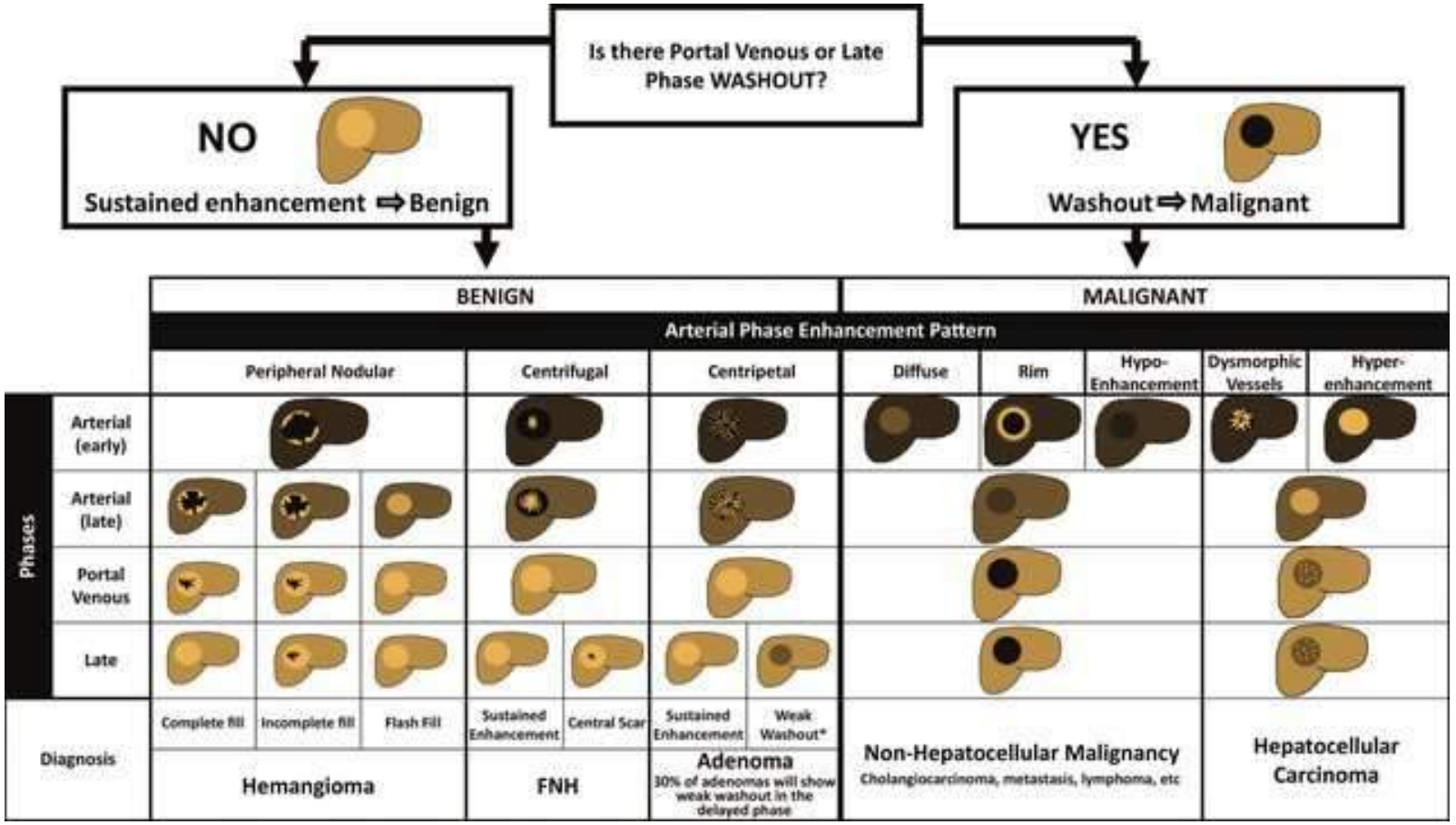
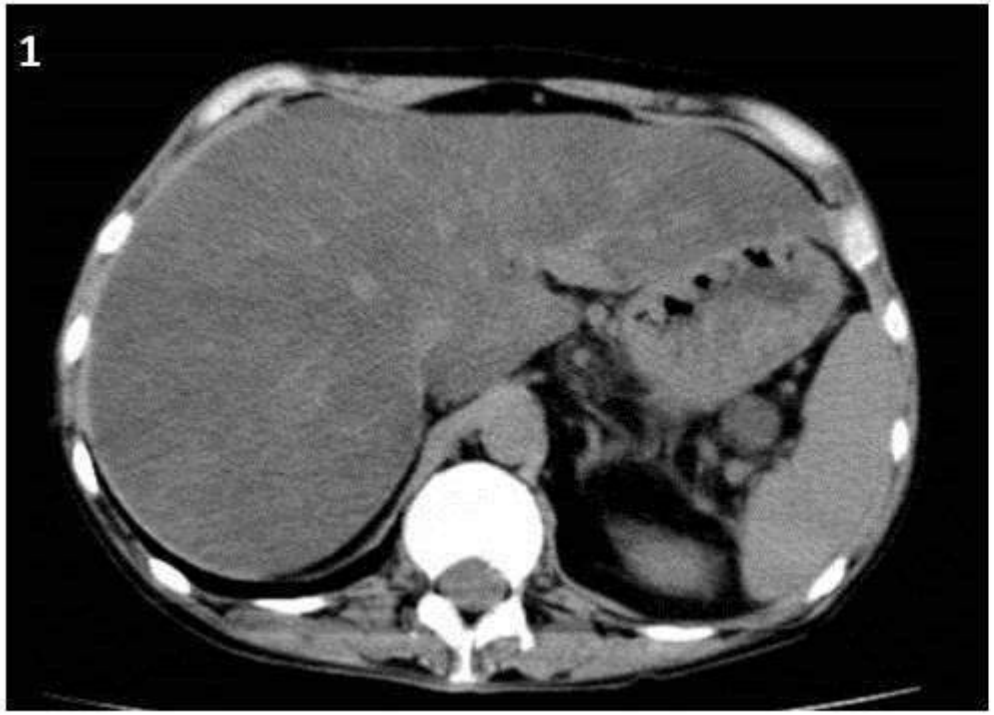


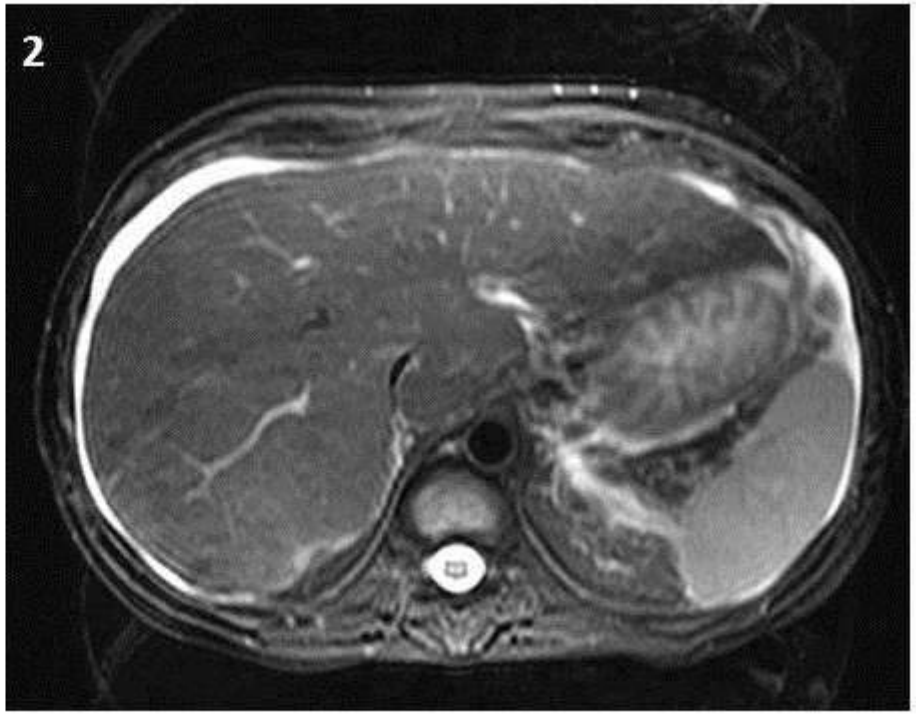
Fig 2 Liver metastases with rapid enhancement in the arterial

Contrast enhanced US (CEUS)



Liver anatomy and pathology CT and MR





Diagnostic accuracy for liver lesions

<1 cm

US 30%

CT 65%

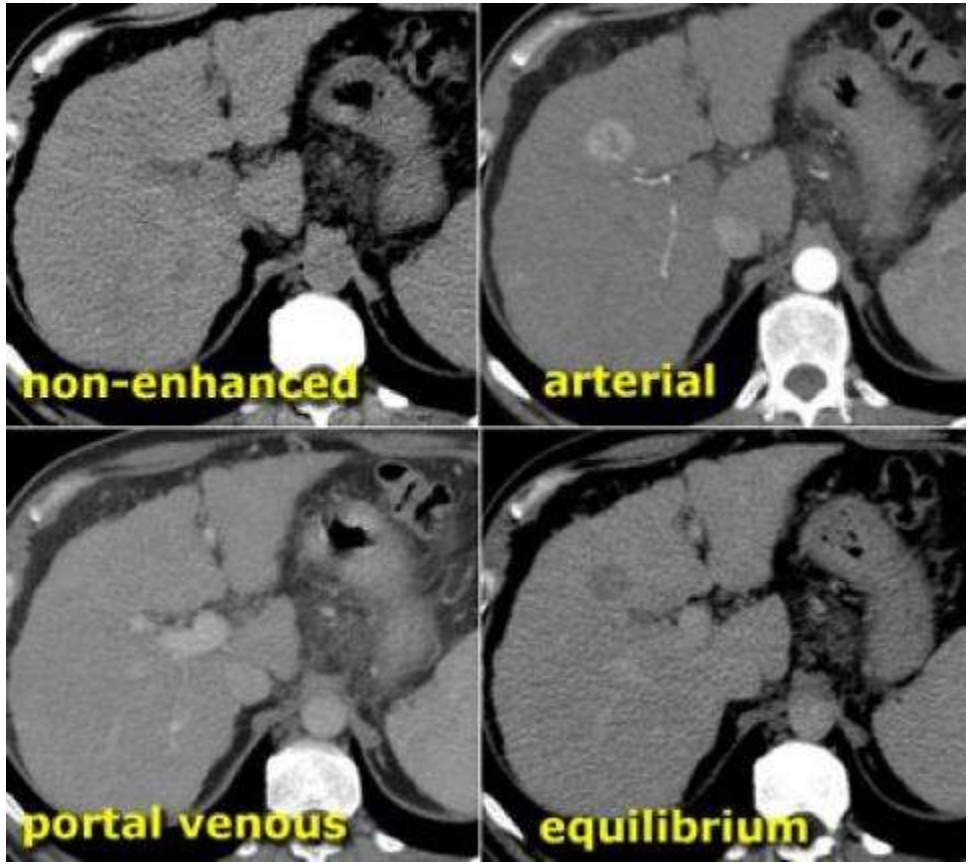
MR 70%

Fiorucci S, Atlante di ecografia in gastroenterologia ed epatologia , 2003

Liver anatomy and pathology CT and MR

Detection of liver masses

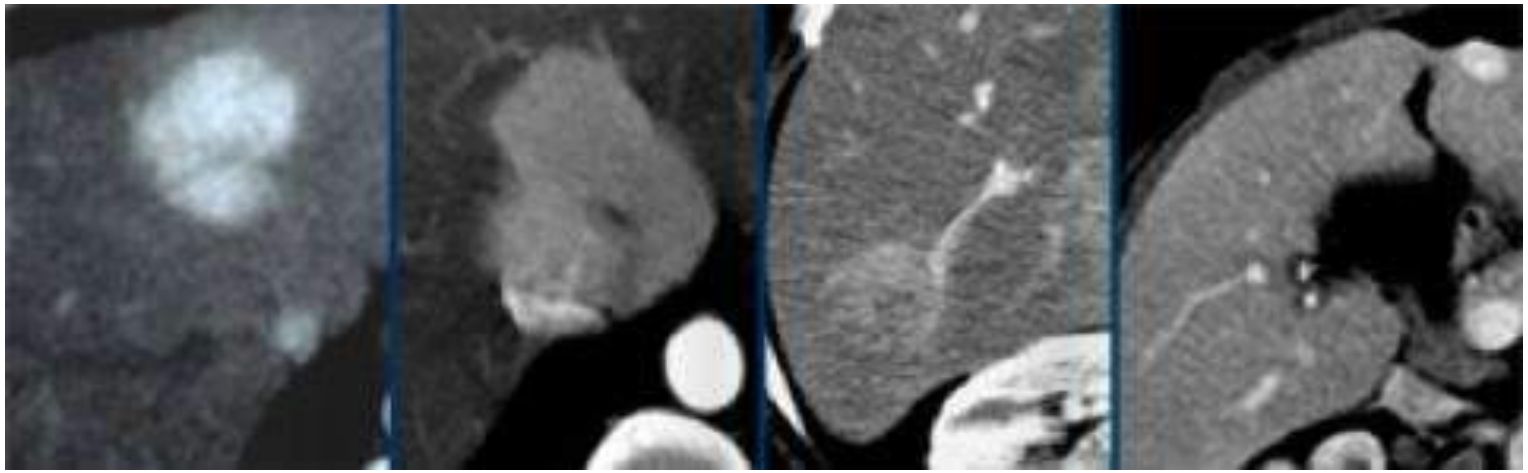
Arterial phase imaging
Portal Venous phase
Equilibrium Phase
Blood pool and Hemangioma
Tailored CT protocol
Characterisation of liver masses
Hypervascular lesions
Hypovascular lesions
Scar
Capsule
Calcifications
Fat
Hemorrhage
Cystic components
Retraction of liver capsule
Peripheral enhancement and progressive fill in



Hypervascular lesions

Arterially enhancing lesions are mostly benign lesions and include primary liver tumors as FNH, adenoma and small hemangiomas that fill rapidly with contrast.

These benign tumors have to be differentiated from the most common hypervascular malignant liver tumor, which is HCC and metastases from hypervascular tumors like melanoma, renal cell carcinoma, breast, sarcoma and neuroendocrine tumors (islet cell tumors, carcinoid, pheochromocytoma).



UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

CLMMC AA 2023/24

Patologia sistematica VI

Gastroenterologia

Prof. Stefano Fiorucci

Liver: clinical biochemistry

Harrison's Principles of Internal Medicine – 19-20° Ed.

Inherited hyperbilirubinemia
- Gilbert's syndrome
- Crigler-Najjar syndrome, types I and II
- Dubin-Johnson syndrome
- Rotor syndrome

Viral hepatitis
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Others (Epstein-Barr virus [mononucleosis] herpesvirus, adenovirus hepatitis)
- Cryptogenic hepatitis

Immune and autoimmune liver diseases
- Primary biliary cirrhosis
- Autoimmune hepatitis
- Sclerosing cholangitis
- Overlap syndromes
- Graft-versus-host disease
- Allograft rejection

Genetic liver diseases
- α$_1$-Antitrypsin deficiency
- Hemochromatosis
- Wilson's disease
- Benign recurrent intrahepatic cholestasis
- Progressive familial intrahepatic cholestasis, types I–III
- Others (galactosemia, tyrosinemia, cystic fibrosis, Niemann-Pick disease, Gaucher's disease)

Alcoholic liver disease
- Acute fatty liver
- Acute alcoholic hepatitis
- Laënnec's cirrhosis

Nonalcoholic fatty liver
- Steatosis
- Steatohepatitis

Acute fatty liver of pregnancy

Liver involvement in systemic diseases
- Sarcoidosis
- Amyloidosis
- Glycogen storage diseases
- Celiac disease
- Tuberculosis
- *Mycobacterium avium-intracellulare* infection

Cholestatic syndromes
- Benign postoperative cholestasis
- Jaundice of sepsis
- Total parenteral nutrition–induced jaundice
- Cholestasis of pregnancy
- Cholangitis and cholecystitis
- Extrahepatic biliary obstruction (stone, stricture, cancer)
- Biliary atresia
- Caroli's disease
- Cryptosporidiosis

Drug-induced liver disease
- Hepatocellular patterns (isoniazid, acetaminophen)
- Cholestatic patterns (methyltestosterone)
- Mixed patterns (sulfonamides, phenytoin)
- Micro- and macrovesicular steatosis (methotrexate, fialuridine)

Vascular injury
- Veno-occlusive disease
- Budd-Chiari syndrome
- Ischemic hepatitis
- Passive congestion
- Portal vein thrombosis
- Nodular regenerative hyperplasia

Mass lesions
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Adenoma
- Focal nodular hyperplasia
- Metastatic tumors
- Abscess
- Cysts

Diagnosis of liver disease

Clinical history
Physical examination
Laboratopry testing
Diagnostic imaging
- US (sonography)
- TC
- RMN

Liver biopsy

Grading and staging of liver diseases

- Non invasive methods of assessing liver fibrosis and cirrhosis (APRI, FIB-4, Fibrotest..)
- Transient elastography
- Child-Pough Classification
- MELD score

Liver biochemistry

Enzymes that reflect damage to hepatocytes

- **Aspartate aminotransferase (AST),** formerly called SGOT. The AST enzyme is also found in muscles and many other tissues besides the liver. **NV <40UI/L**
- **Alanine aminotransferase (ALT)**, formerly called SGPT. ALT is almost exclusively found in the liver. **NV < 40UI/L**

- AST/ALT >1000 UI/L occurs in extensive acute liver injury
- AST/ALT a ratio of 2-4 folds of normal occurs in chronic hepatitis
- AST:ALT ratio 2:1 is suggestive of alcoholic liver disease

Liver biochemistry:

Enzymes that reflect damage to hepatocytes

Chronic, Mild Elevations, ALT > AST
(<150 U/L or 5 × normal)
Hepatic Causes
α_1-Antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B, C, and D)
Hemochromatosis
Medications and toxins
Steatosis and steatohepatitis
Wilson disease

Nonhepatic Causes
Celiac disease
Hyperthyroidism

Severe, Acute Elevations, ALT > AST
(>1000 U/L or >20-25 × normal)
Hepatic Causes
Acute bile duct obstruction
Acute Budd-Chiari syndrome
Acute viral hepatitis
Autoimmune hepatitis
Drugs and toxins
Hepatic artery ligation
Ischemic hepatitis
Wilson disease

Severe, Acute Elevations, AST > ALT
(>1000 U/L or >20-25 × normal)
Hepatic Cause
Medications or toxins in a patient with underlying alcoholic liver injury

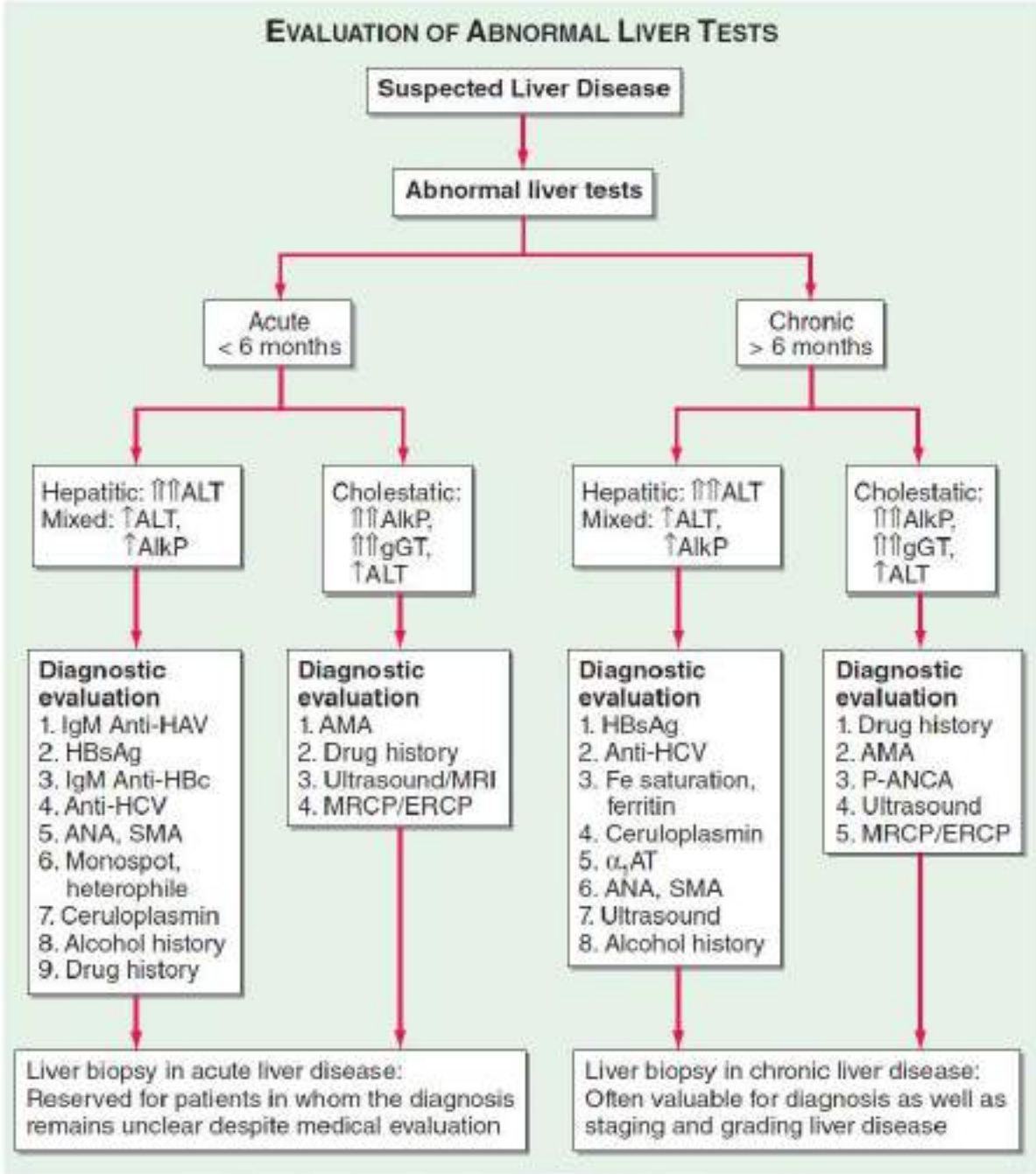
Nonhepatic Cause
Acute rhabdomyolysis

Chronic, Mild Elevations, AST > ALT
(<150 U/L, <5 × normal)
Hepatic Causes
Alcohol-related liver injury (AST/ALT > 2:1, AST nearly always <300 U/L)
Cirrhosis

Nonhepatic Causes
Hypothyroidism
Macro-AST
Myopathy
Strenuous exercise

*Virtually any liver disease can cause moderate aminotransferase elevations (5-15 × normal).

AST= SGOT
ALT=SGPT



Algorithm for evaluation of abnormal liver tests.

Source: Harrison's Principles of Internal Medicine (19th Ed)

Liver clinical biochemistry

Tests that measure the biosynthetic activity of the liver

- **Serum Albumin:** levels are low in severe chronic liver diseases, because reduced protein synthesis. **NV >3.5 g/l**
- **Serum globulins:** γ globulins are produced by B lymphocytes and α andβ by hepatocytes. γ globulins increases in several liver diseases acute and chronic.

Liver clinical biochemistry

Tests that measure the biosynthetic activity of the liver

-

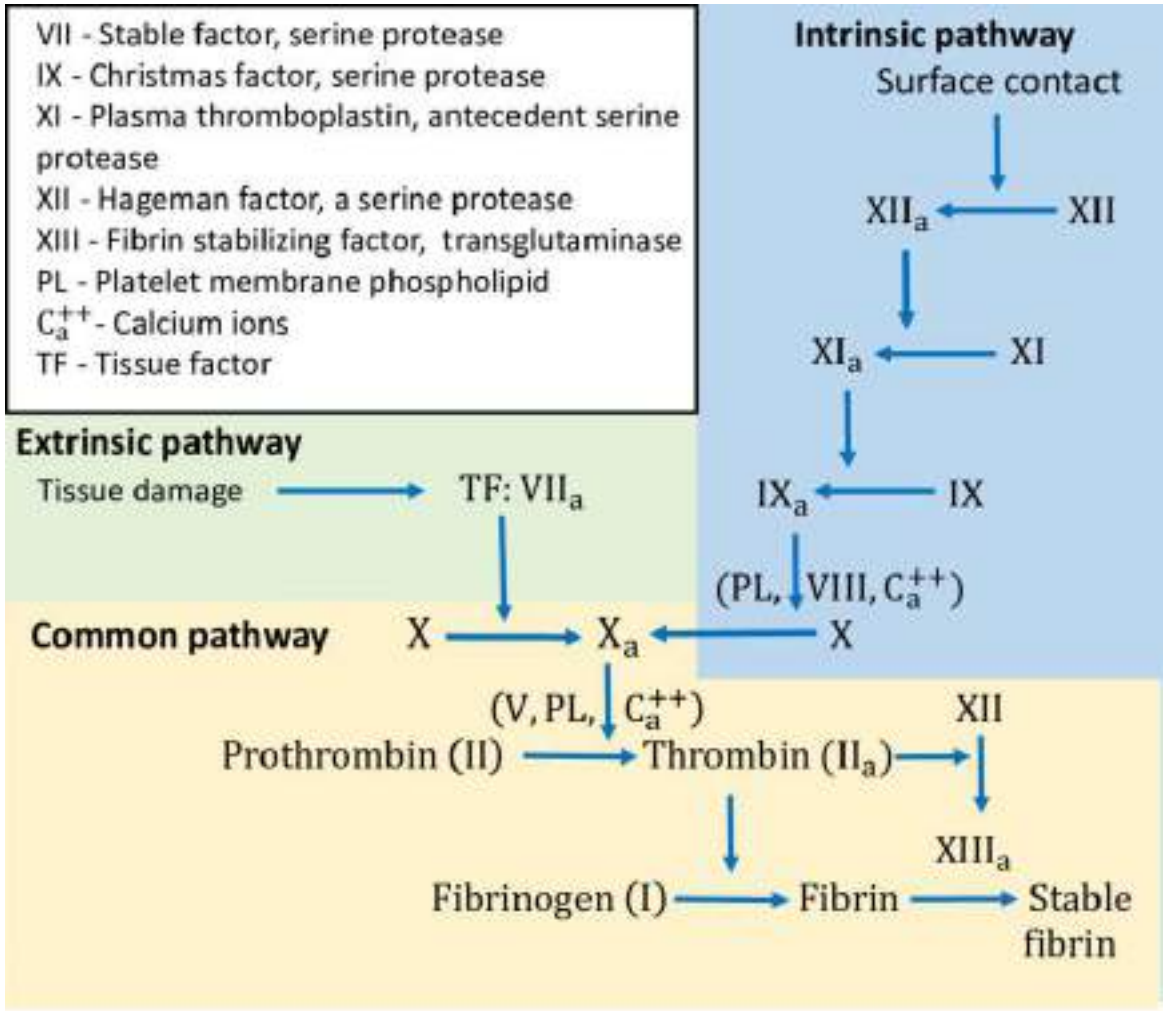
COAGULATION FACTORS

With the the exception of the Factor VIII, which is produced by vascular endothelial cells, the blood clotting factors are produced exclusively by the liver.

- **Prothrombin time (PT):** A test of the time it takes for a blood sample to clot, under specific conditions in a lab. If low levels of clotting factors are present, the prothrombin time is longer **NV 70-100%**
- **International normalized ratio** (INR): a standardized way for all labs to report PT, so their results can be compared accurately with each other **>1.3**

Prothrombin time

Measures the activity of factor I (Fibrinogen), II (Prothrombin), V (Proaccelerin), VII (Proconvertin), and X (Stuart–Prower Factor)



Causes of Abnormal Prothrombin Time

- Deficiencies of Factor VII
- Deficiencies of Factor X
- Deficiencies of Factor V
- Deficiencies of Factor II
- Deficiencies of Fibrinogen
- Heparin
- Warfarin
- Fibrinogen/Fibrin Degradation Products
- Lupus Anticoagulant
- Liver Disease

Liver clinical biochemistry

Tests that measure the biosynthetic activity of the
Test reflecting detoxification and excretion

Bilirubin

Indirect or unconjugated bilirubin

0.2-0.4 mg/dl

Direct bilirubin or conjugated

0.4-0.6 mg/dl

Total bilirubin

<1.2 mg/dl

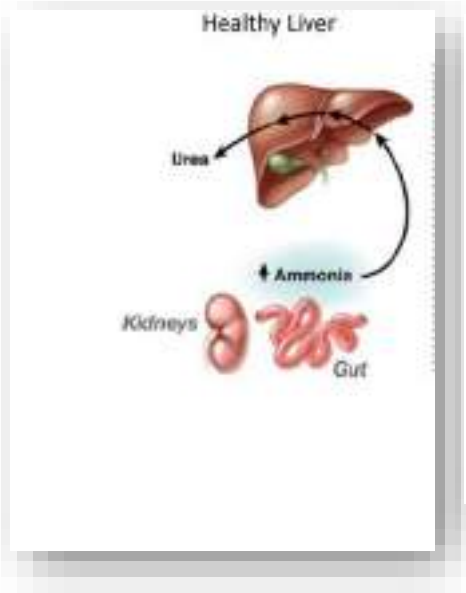
Jaundice may be noticeable in mucosas at levels of 2 to 3 mg/dL and in the skin at higher levels.

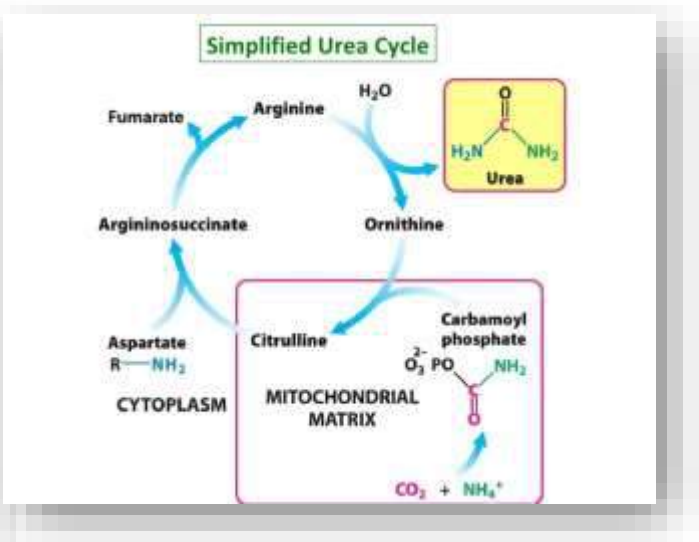
Urine urobilinogen (see below)

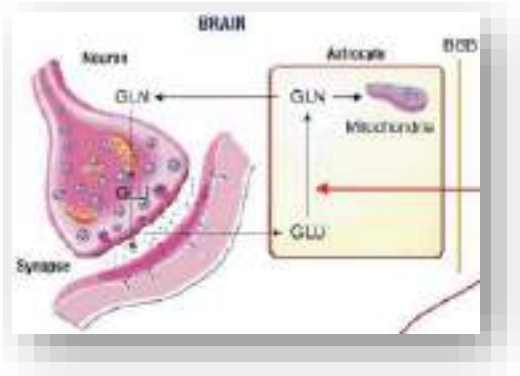
Liver clinical biochemistry

Test reflecting detoxification and excretion

Ammonia is produced in the body during normal protein metabolism and by colon bacteria and recycled in the liver to generate urea.







Increased blood levels of ammonia associates to hepatic encelophathy

Liver clinical biochemistry

Enzymes that reflect cholestasis

- **Alkaline phosphatase** NV <120-180 UI/L
- **Gamma-glutamyl transpeptidase** (γGT) NV<50UI/L
- **5-nucleotidase**
- **Bilirubin** (also indicates reduced detoxification ability)
- **Urine bilirubin** urobilinogen 1-3 mg/dl

Liver clinical biochemistry

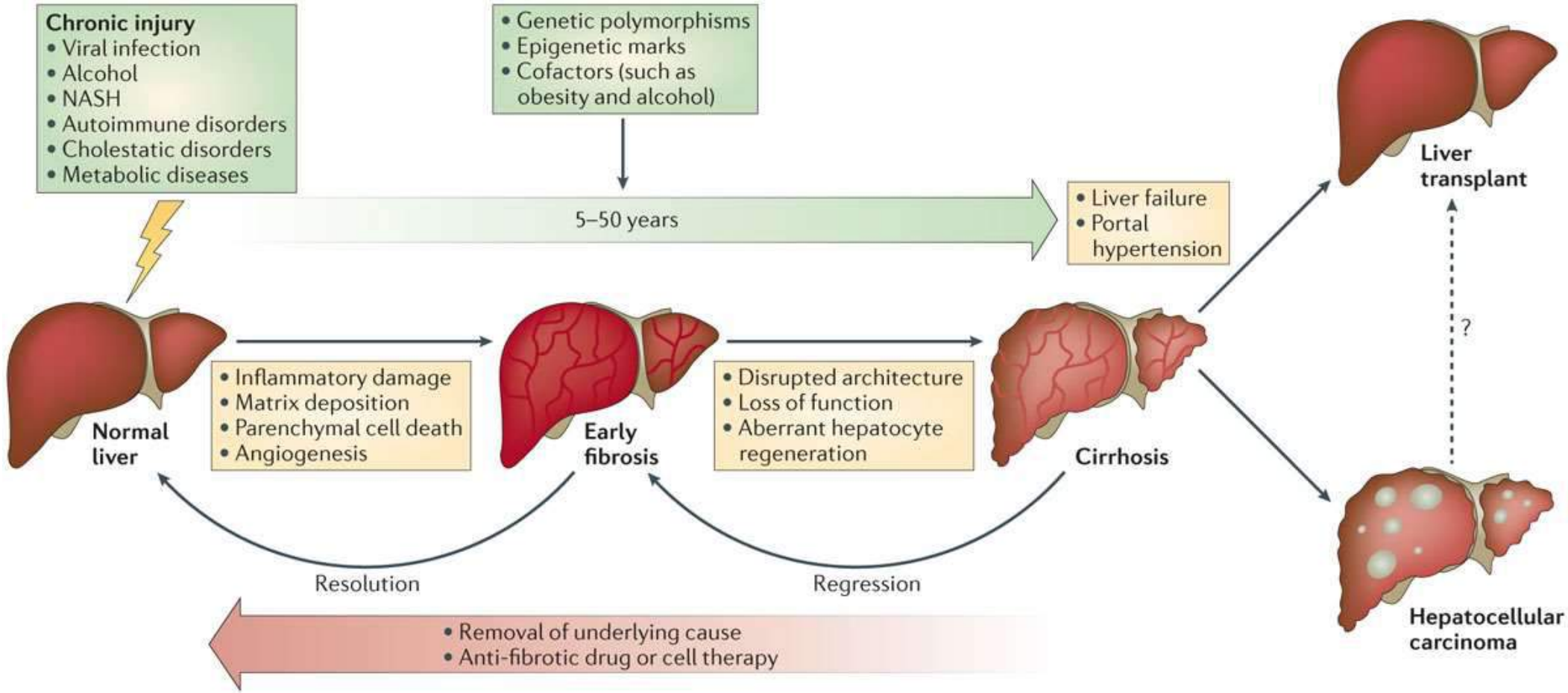
TABLE 358-1 LIVER TEST PATTERNS IN HEPATOBILIARY DISORDERS

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU, ALT > AST	Normal to <3× normal elevation	Normal	Usually normal. If >5× above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis, cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT >2 suggests alcoholic hepatitis or cirrhosis	Normal to <3× normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis	Both fractions may be elevated	Normal to moderate elevation	Elevated, often >4× normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
(Obstructive jaundice)	Bilirubinuria	Rarely >500 IU		Normal	Normal
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation	Elevated, often >4× normal elevation Fractionate, or confirm liver origin with 5'-nucleotidase or γ glutamyl transpeptidase		

Liver fibrosis

is the main determinant of patients outcome in many liver chronic diseases

Liver fibrosis is the main determinant of patients outcome



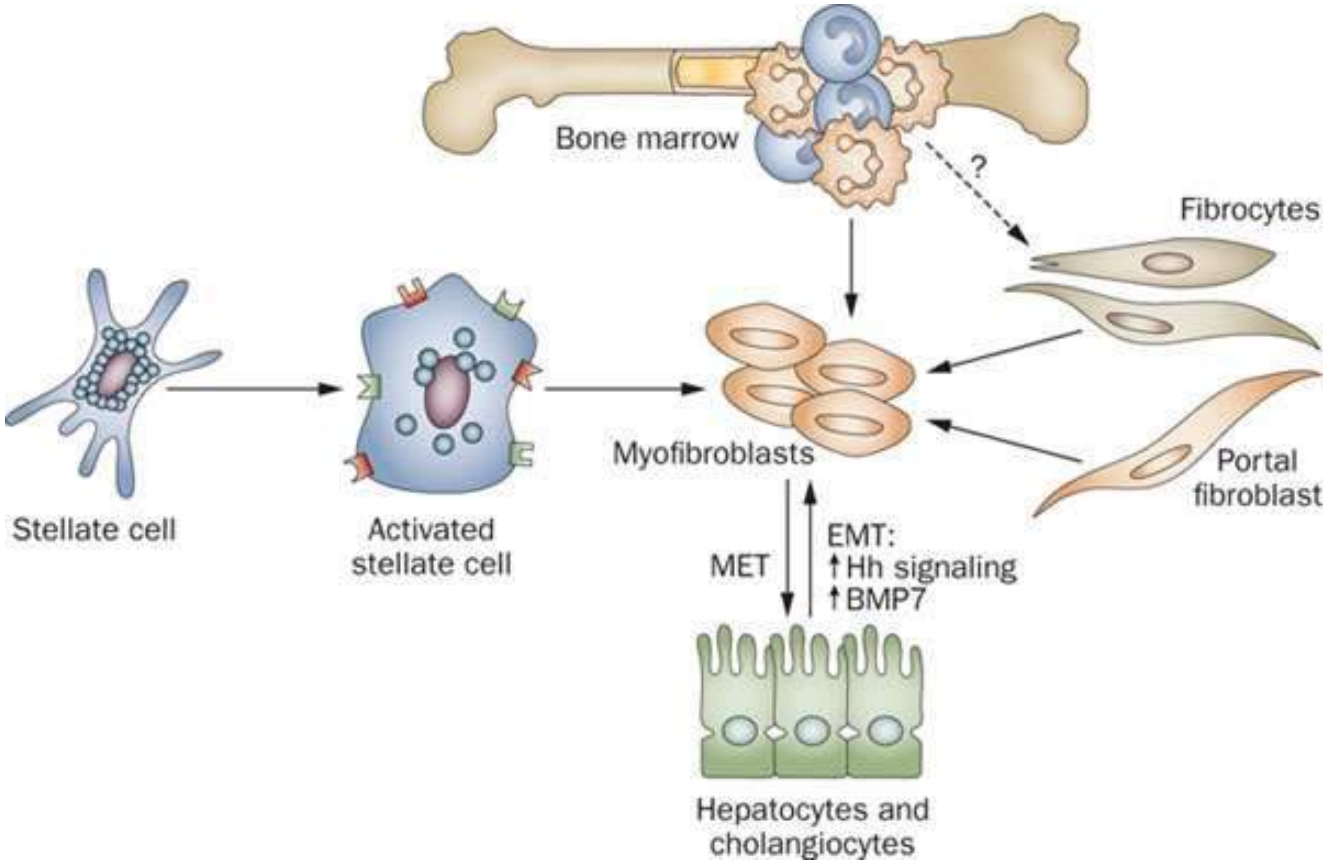
Nature Reviews | Immunology

Assessing Liver fibrosis

Liver fibrosis is a pathological state that occurs in crhonic liver disorders and is associated **with increased risk of progression toward liver cirrhosis and predict poor prognosis**

Liver fibrosis is caused by activation of **hepatic stellate cells** (or Ito cells) and mesenchymal cells in response to liver injury.

Sources of fibrogenic cell types in hepatic fibrosis



Friedman, S. L. (2010) Evolving challenges in hepatic fibrosis
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2010.97

Liver fibrosis

Assessment of liver fibrosis is obtained by:

- **Biochemistry (APRI, FIB-4, etc)**
- **Transient elastography**
- **MR**
- **Liver biopsy**

Liver fibrosis: biochemical scores

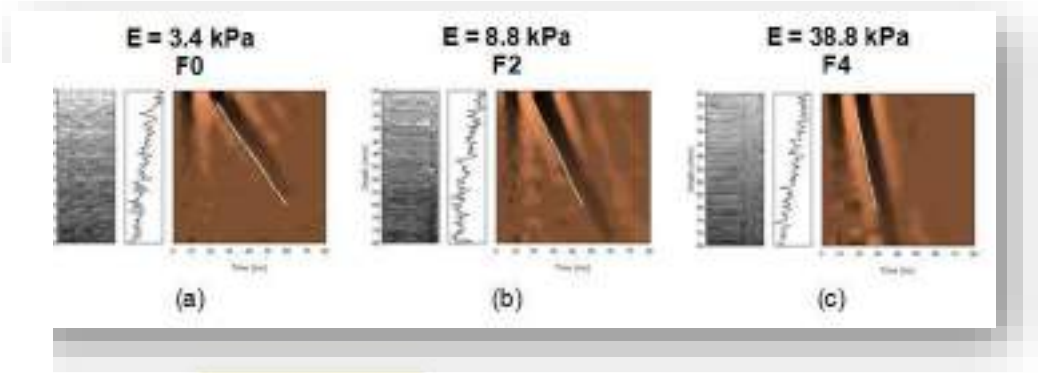
FIB-4: Age, AST, ALT Platelet count

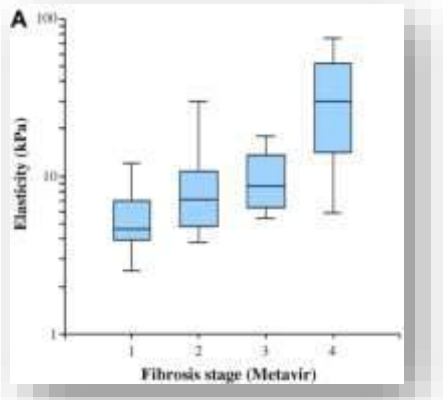
APRI: AST, platelet count

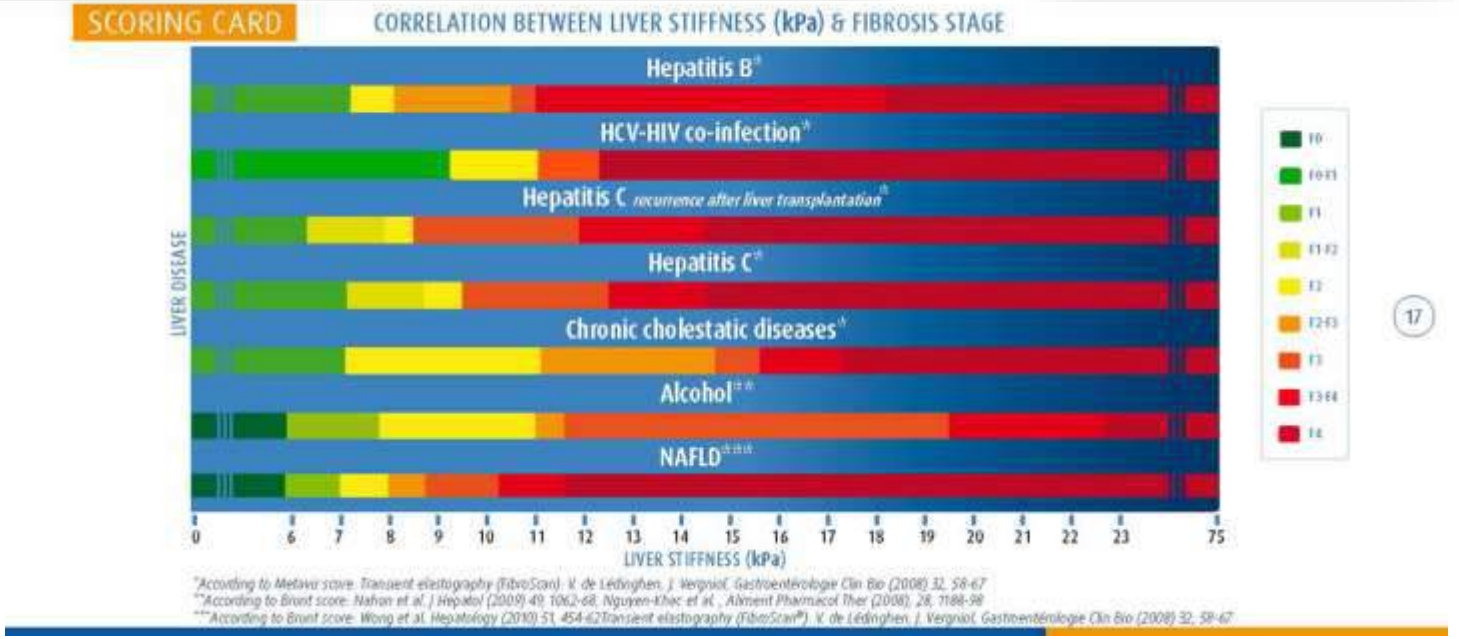
Fibro test The test incorporate :
Haptoglobin, bilirubin, γGT, apo-lipoprotein A1 and α2 – macroglobulin

ELF: Age, hyaluronic acid, MMP3, TIMP1

Transient elastography





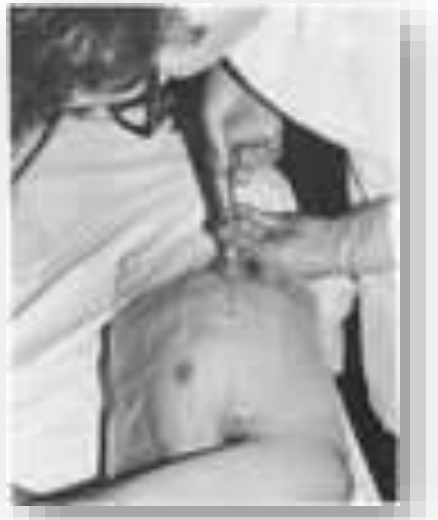


Liver biopsy

LANDMARKS IN HEPATOLOGY

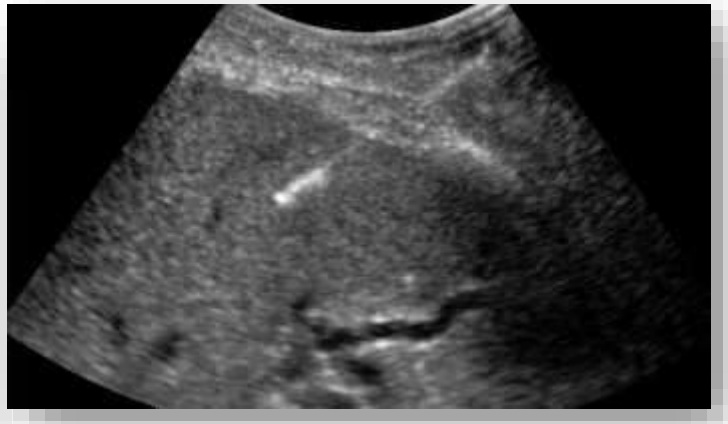
Just A Second

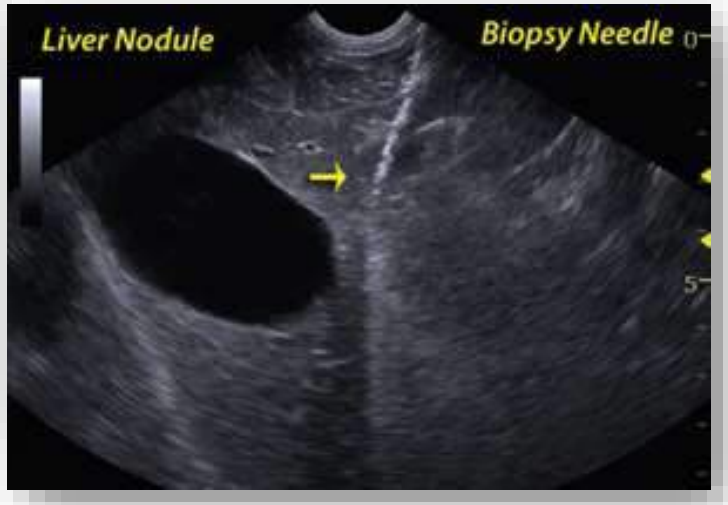
Fig. 1. Top: 7-cm × 1.6-mm Menghini needle c.1958, complete with skin-piercing stylet (above) and 3.5-cm "nail" shown partially inserted into the hub. A generous gift from Dr. Lee Sataline (Cheshire, CT). Middle: Diagrammatic representation of the successive steps of the Menghini technique of liver biopsy (reprinted with permission from the American College of Gastroenterology[33]). Bottom: Giorgio Menghini (2/14/1916-10/25/1983) in 1982. Photograph courtesy of Professore Stefano Fiorucci, provided by Menghini's daughter Chiara.

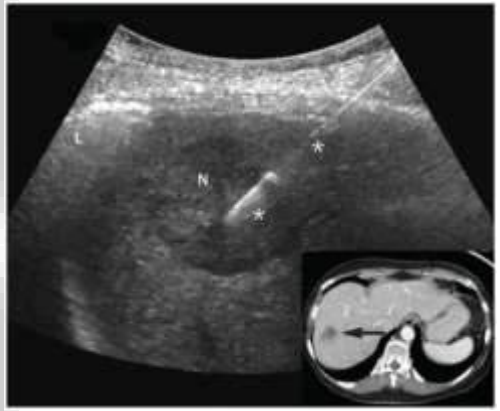


31. Menghini G. One-second needle biopsy of the liver. Gastroenterology 1958;35:190-199.
32. Menghini G. One-second biopsy of the liver—problems of its clinical application. N Engl J Med 1970;283:582-585.
33. Menghini G, Lauro G, Caracenti M. Some innovations in the technic of the one-second needle biopsy of the liver. Am J Gastroenterol 1975;64: 175-180.

Liver biopsy



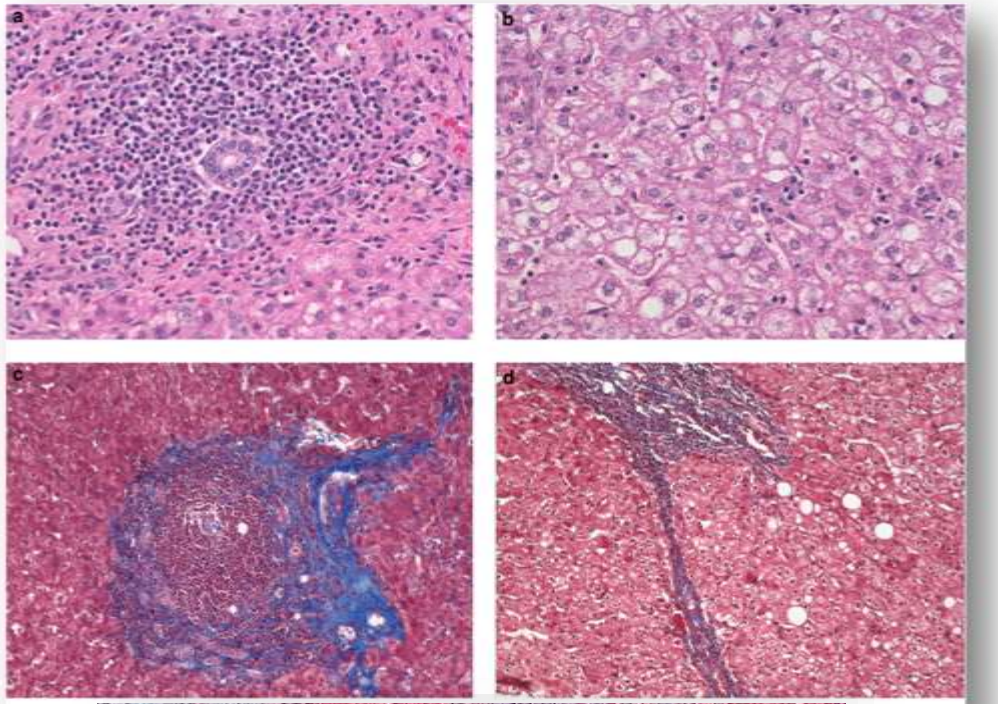


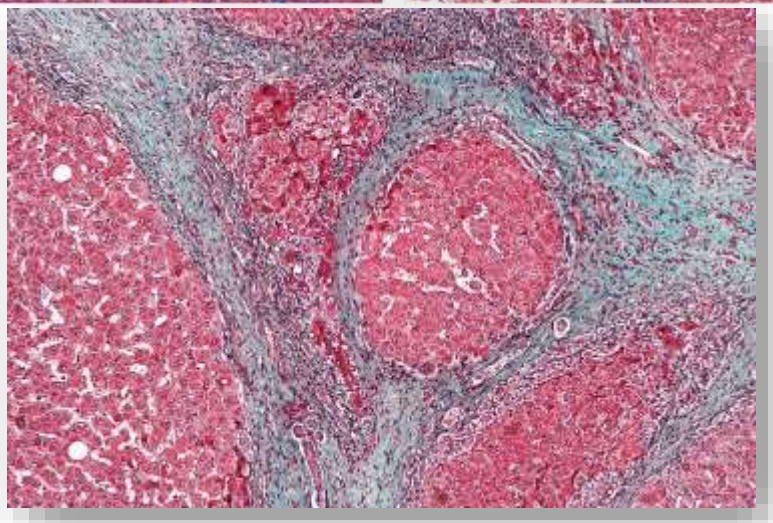


Liver Biopsy.mp4

EUS-FNA technique for subcapsular liver mets.avi.mp4

Liver histology





NAFLD activity score

Steatosis
- < 5%: 0
- 5–33%: 1
- 34–66%: 2
- > 66%: 3

Lobular inflammation
- None: 0
- < 2: 1
- 2–4: 3
- > 4: 4

Ballooning of hepatocytes
- None: 0
- Few ballooned: 1
- Many ballooned: 2

NAS score (0–8)
- < 3: not NASH
- ≥ 5: NASH

NASH fibrosis stage

Stage 0
No fibrosis

Stage 1
Zone 3 perisinusoidal fibrosis
- Mild – 1a
- Moderate – 1b
- Portal/periportal – 1c

Stage 2
Perisinusoidal and portal/ periportal fibrosis

Stage 3
Bridging fibrosis

Stage 4
Cirrhosis

Grading and staging liver diseases

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

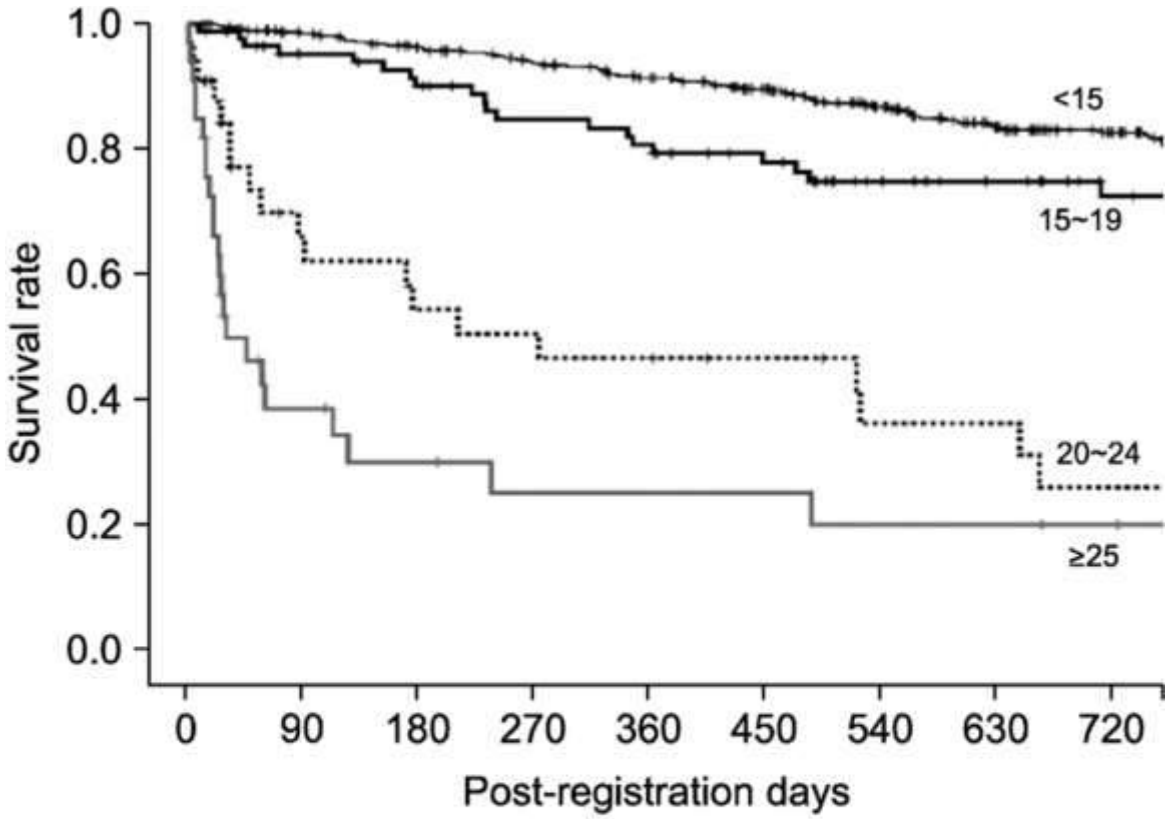
Grading and staging liver diseases

Model for End-Stage Liver Disease (MELD) Score

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

NOTES:

- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)



	No.	14 day	30 day	3 mo	1 yr	2 yr	3 yr
MELD<15	385	100.0%	99.5%	98.4%	91.4%	82.6%	74.7%
MELD, 15~19	86	98.8%	98.8%	95.2%	79.3%	72.4%	72.4%
MELD, 20~24	33	90.9%	84.2%	65.9%	46.5%	25.9%	
MELD≥25	33	81.8%	53.3%	38.5%	25.0%	20.0%	

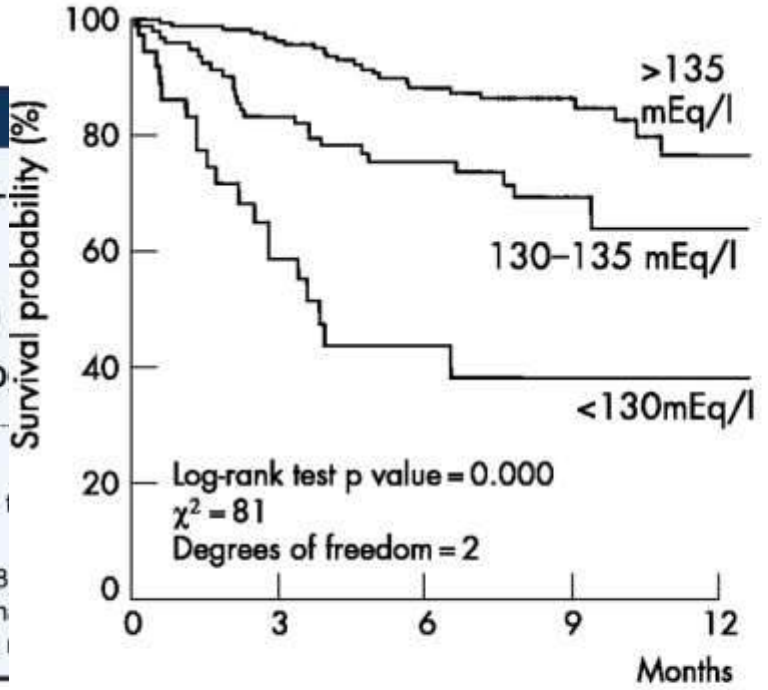
Grading and staging liver diseases
Na+

Model for End-Stage Liver Disease (MELD) Score

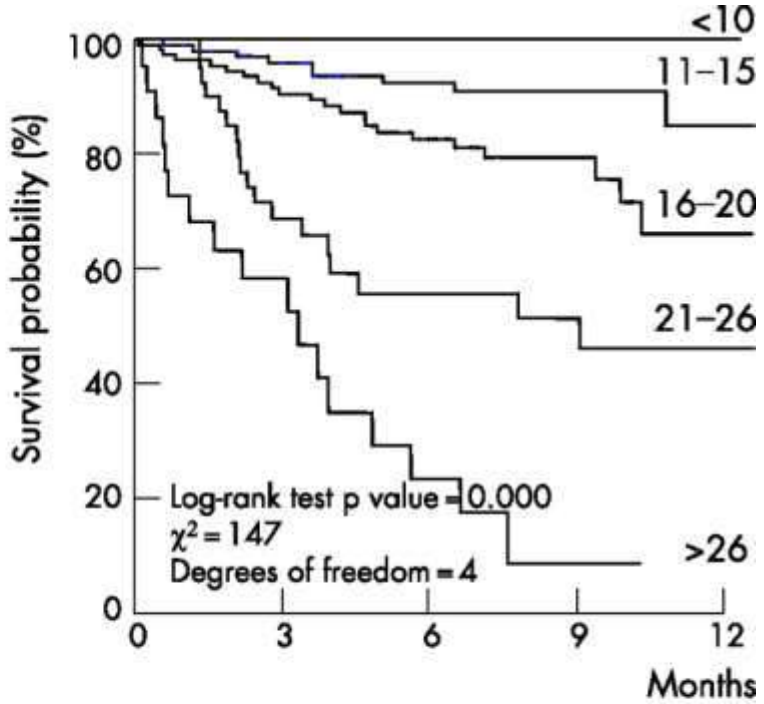
MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL)
6.43 (constant for liver disease etiolo

NOTES:

- If the patient has been dialyzed twice within the last 7 days, then t for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8 of 1.0 is used) to prevent the occurrence of scores below 0 (the n logarithm of 1 is 0, and any value below 1 would yield a negative



Serum sodium>135 mEq/l (n = 173)
Serum sodium 131–135 mEq/l (n = 98)
Serum sodium<130 mEq/l (n = 37)



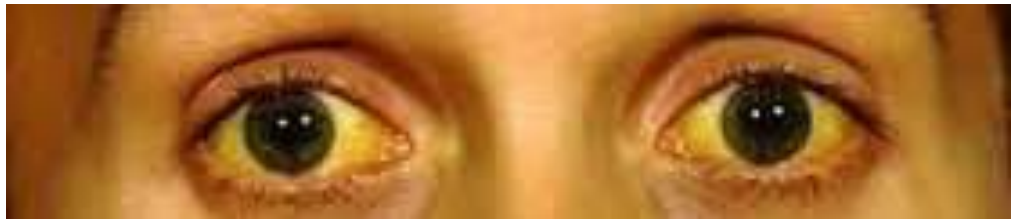
MELD <10 (n = 13)
MELD 11–15 (n = 105)
MELD 16–20 (n = 116)
MELD 21–26 (n = 41)
MELD <26 (n = 23)

Grading and staging liver diseases

MELD-derived models [Ref]	Equations	Strengths	Limitations
			For all the scores including serum Na: rapid spontaneous and iatrogenic Na variability
MELD-Na [74]	MELD + 1.59 × (135 – Na)	More accurate in 6-month mortality prediction	Derived from a retrospective study, not validated, limited number of deaths during the follow-up period
MELD-Na [89]	MELD – Na – [0.025 × MELD × (140 – Na)] + 140	More accurate in 3-month mortality prediction Validated in a large population	Derived from a retrospective study, based on a non-specific database (waiting-list registry)
iMELD [90]	MELD + (age × 0.3) − (0.7 × Na) + 100	More accurate 3-, 6-, and 12-month mortality prediction	Derived from a retrospective study, validation group including HCC Advantages older recipients, who show lower post-OLT patient and graft survival
UKELD [39]	[(5.395 × ln(INR)) + (1.485 × ln(creatinine)) + (3.13 x ln(bilirubin)) −(81.565 × ln(Na))] + 435	Validated in a separate prospective cohort	Derived from a retrospective study, lack of data for comparison with MELD
MESO [94]	MELD / Na	Higher predictive value than MELD	Derived from a retrospective study, not tested on a waiting list population
MELD-AS [71]	MELD + 4.46 (if persistent ascites) + 4.53 (if Na <135)	Identifies patients with high mortality risk despite low MELD score	Derived from a retrospective study, not superior to standard MELD with scores ≥21
Updated MELD [55]	1.266 × ln(1 + creatinine) + 0.939 x ln(1+bilirubin) + 1.658 × ln(1 + INR)	More accurate 3-month and and overall predictor of mortality Derived from a large sample size	Derived from a retrospective study, based on a non-specific database (waiting-list registry)
Δ MELD [96, 97]	$MELD_2 - MELD_1$	Dynamic evaluation of disease progression	Derived from a retrospective study, time interval between assessment not defined

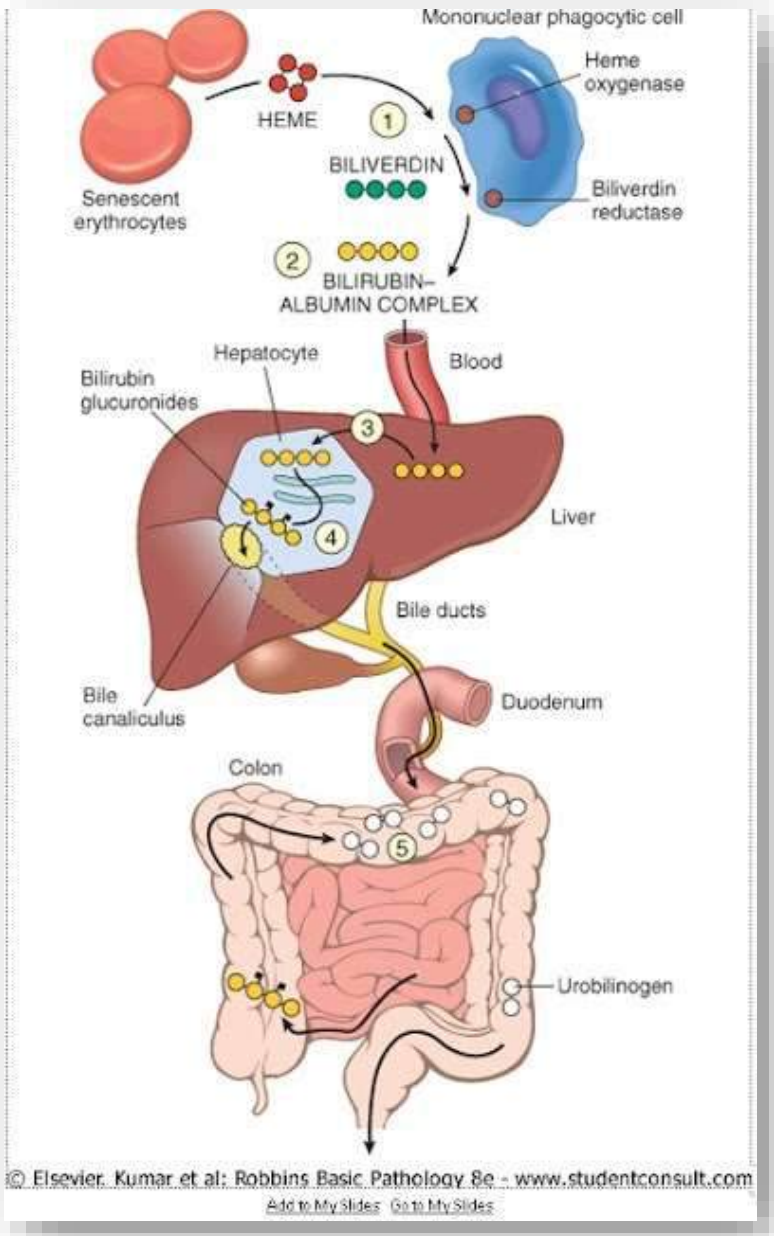
Jaundice

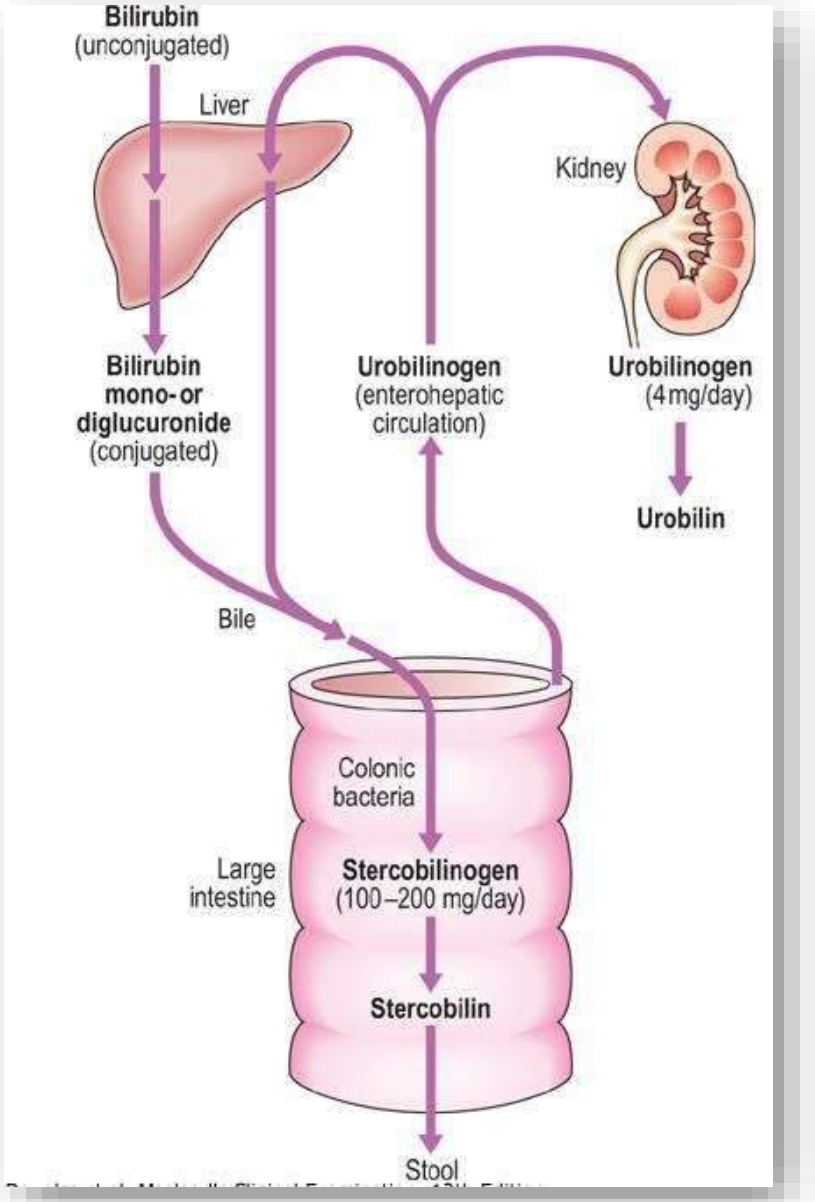
Jaundice is a yellowish discoloration of the skin and other membranes including sclerae and mucus membrane caused by hyperbilirubinemia.

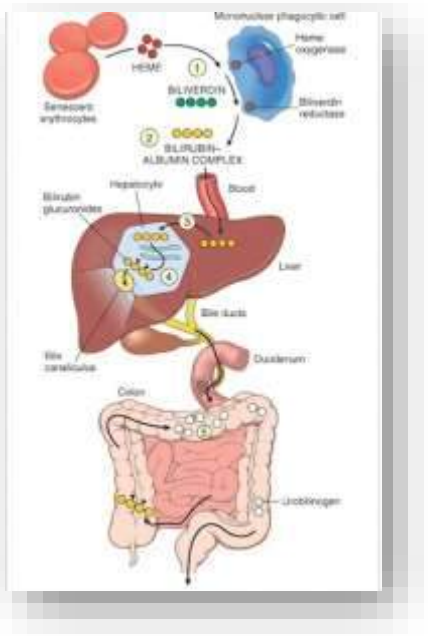


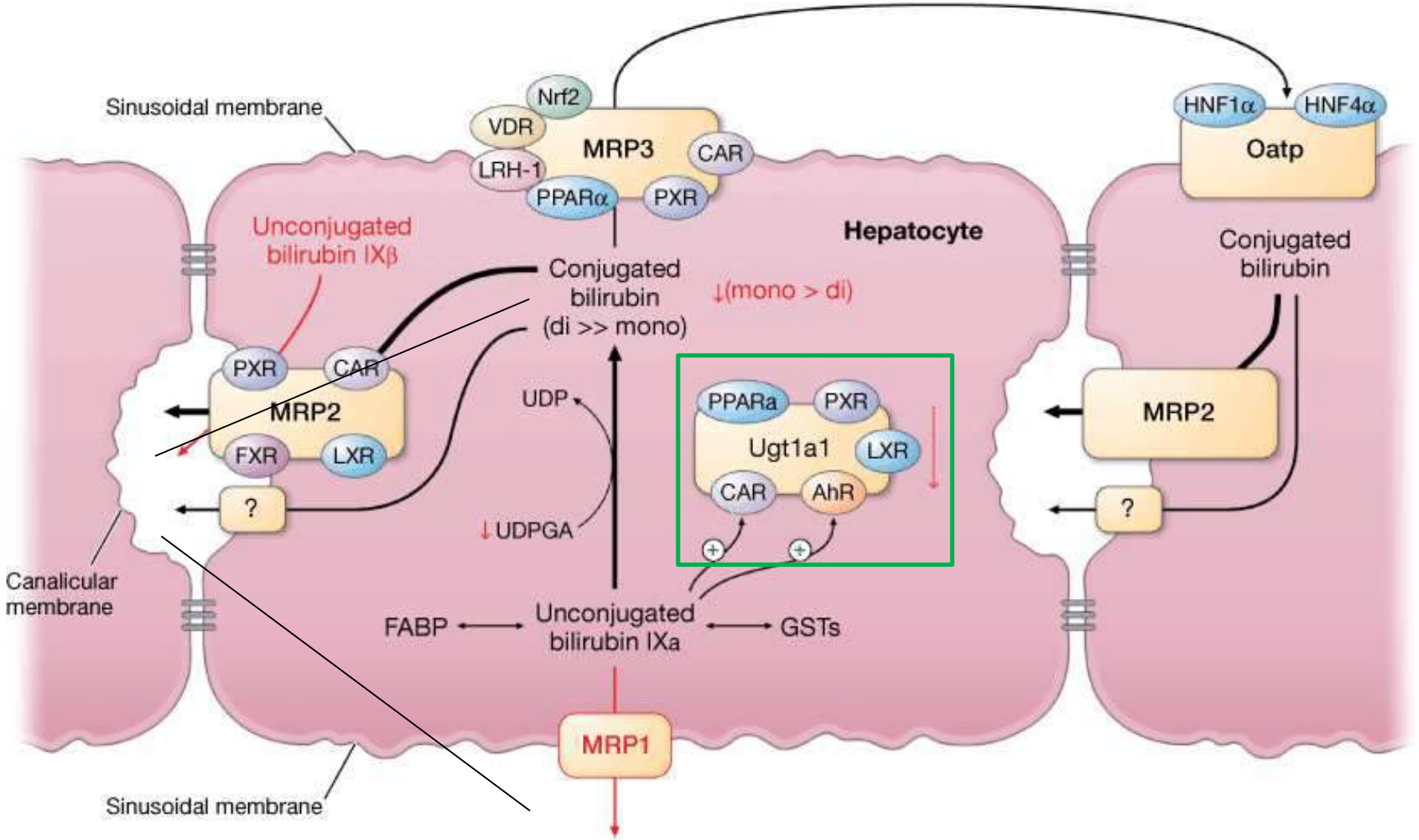
Hyperbilirubinamia is a sign of liver diseases or less frequently of a hemolytic disorder

Bilirubin metabolism

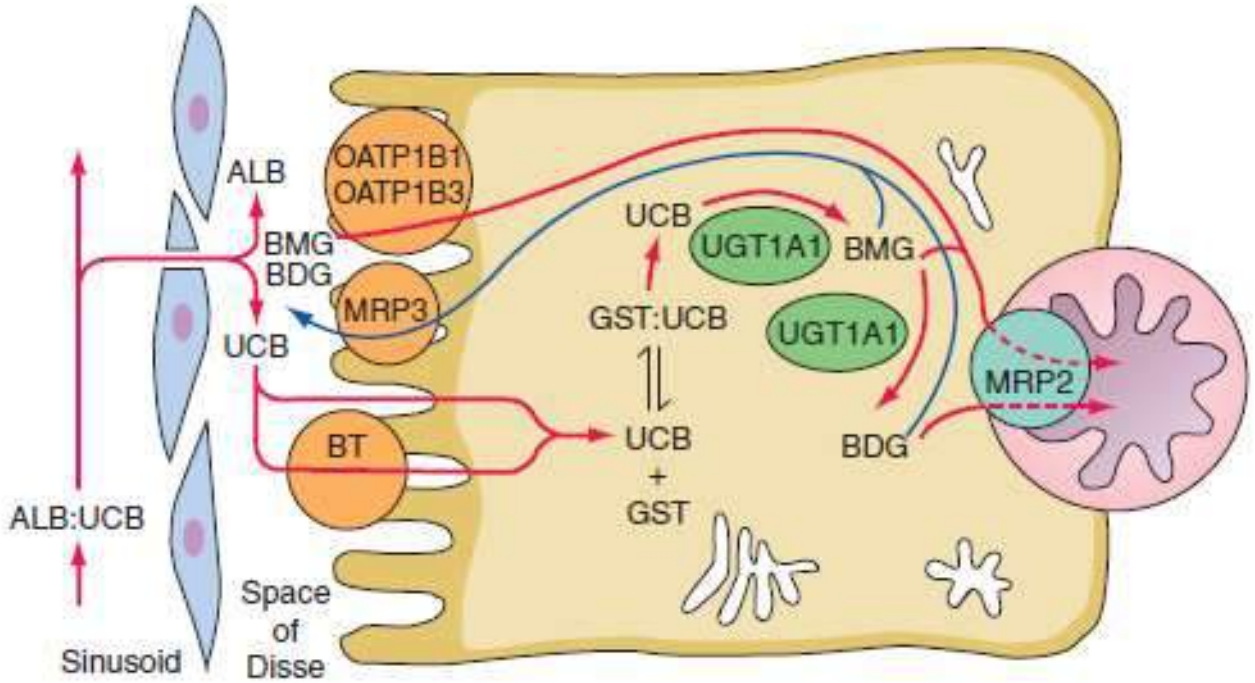








epatocellular bilirubin transport.
lbumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional rocesses.
Within the cell it is bound to **glutathione-S-transferases and conjugated by bilirubin-UDP-glucuronosyltransferase (UGT1A1) to mono- and diglucuronides, which are ctively transported across the canalicular membrane into the bile.** ALB, albumin; UCB, unconjugated bilirubin, UGT1A1, bilirubin-UDP-glucuronosyltransferase; BMG, ilirubin monoglucuronide; GST, glutathione-S-transferase; MRP2, multidrug resistance–associated protein 2; BDG, bilirubin diglucuronide; BT, proposed bilirubin transporter.



Hepatocellular bilirubin transport.

Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes.

Within the cell it is bound to **glutathione-S-transferases and conjugated by bilirubin-UDP-glucuronosyltransferase (UGT1A1)** to mono- and diglucuronides, which are actively transported across the canalicular membrane into the bile. ALB, albumin; UCB, unconjugated bilirubin, UGT1A1, bilirubin-UDP-glucuronosyltransferase; BMG, bilirubin monoglucuronide; GST, glutathione-S-transferase; MRP2, multidrug resistance–associated protein 2; BDG, bilirubin diglucuronide; BT, proposed bilirubin transporter.

Jaundice

Bilirubin

The bilirubin present in serum represents a balance between input from production of bilirubin and hepatic/biliary removal of the pigment.

Hyperbilirubinemia may result from

1. **overproduction of bilirubin;**
2. **impaired uptake, conjugation, or excretion of bilirubin;**
3. **Defect of excretion and regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts.**

Clinical approach to jaundice

- An increase in **unconjugated bilirubin** in serum results from either overproduction, impairment of uptake, or conjugation of bilirubin.

- An increase in **conjugated bilirubin** is due to decreased excretion into the bile ductules or backward leakage of the pigment.

Causes of Isolated Hyperbilirubinemia

I. Indirect hyperbilirubinemia

A. Hemolytic disorders

1. **Inherited**:

Spherocytosis, elliptocytosis, Glucose-6-phosphate dehydrogenase and pyruvate kinase deficiencies or sickle cell anemia

2. Acquired

- a. Microangiopathic hemolytic anemias, Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia, Immune hemolysis
- B. Ineffective erythropoiesis, 1. Cobalamin, folate, thalassemia, and severe iron deficiencies

C. Drugs

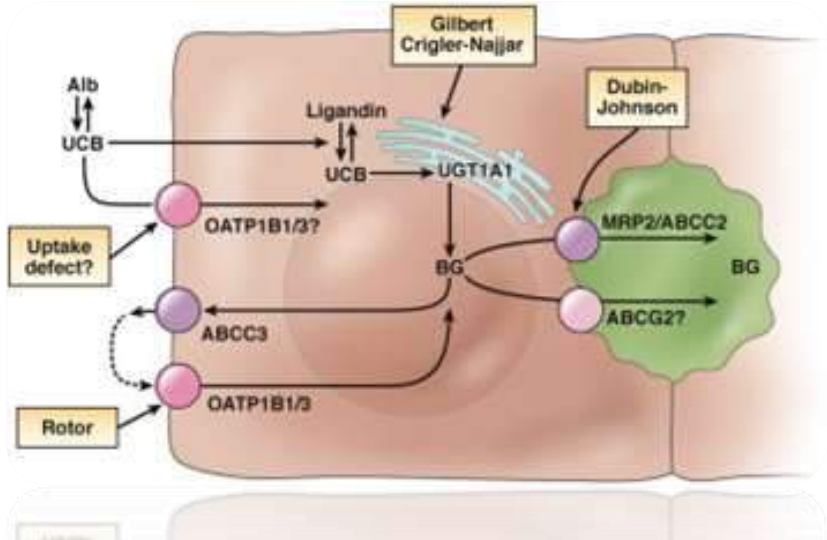
- 1. Rifampicin, probenecid, ribavirin

D. Inherited conditions

- 1. Crigler-Najjar types I and II
- 2. Gilbert's syndrome

II. Direct hyperbilirubinemia

- A. Inherited conditions
- 1. Dubin-Johnson syndrome
- 2. Rotor's syndrome



Main clinical syndromes caused by a deficit of UDP1-glucuronosyltrasnferase

TABLE 359-1 PRINCIPAL DIFFERENTIAL CHARACTERISTICS OF GILBERT AND CRIGLER-NAJJAR SYNDROMES

	Crigler-Najjar Syndrome		
Feature	**Type I**	**Type II**	**Gilbert Syndrome**
Total serum bilirubin, μmol/L (mg/dL)	310–755 (usually >345) (18–45 [usually >20])	100–430 (usually ≤345) (6–25 [usually ≤20])	Typically ≤70 μmol/L (≤4 mg/dL) in absence of fasting or hemolysis
Routine liver tests	Normal	Normal	Normal
Response to phenobarbital	None	Decreases bilirubin by >25%	Decreases bilirubin to normal
Kernicterus	Usual	Rare	No
Hepatic histology	Normal	Normal	Usually normal; increased lipofuscin pigment in some
Bile characteristics			
Color	Pale or colorless	Pigmented	Normal dark color
Bilirubin fractions	>90% unconjugated	Largest fraction (mean: 57%) monoconjugates	Mainly diconjugates but monoconjugates increased (mean: 23%)
Bilirubin UDP-glucuronosyltransferase activity	Typically absent; traces in some patients	Markedly reduced: 0–10% of normal	Reduced: typically 10–33% of normal
Inheritance (all autosomal)	Recessive	Predominantly recessive	Promoter mutation: recessive Missense mutations: 7 of 8 dominant; 1 reportedly recessive

Isolated hyperbilirubinemia: unconjugated bilirubin

Physiologic neonatal jaundice

Bilirubin produced by the fetus is cleared by the placenta and eliminated by the maternal liver. Immediately after birth, the neonatal liver must assume responsibility for bilirubin clearance and excretion. However, many hepatic physiologic processes are incompletely developed at birth.

Levels of UGT1A1 are low, and alternative excretory pathways allow passage of unconjugated bilirubin into the gut. Since the intestinal flora that convert bilirubin to urobilinogen are also undeveloped, an enterohepatic circulation of unconjugated bilirubin ensues. As a consequence, most neonates develop mild unconjugated hyperbilirubinemia between days **2 and 5 after birth. Peak levels are typically 5–10 mg/dL and decline to normal adult concentrations within 2 weeks, as mechanisms required for bilirubin disposition mature.**

Prematurity, often associated with more profound immaturity of hepatic function and hemolysis, can result in higher levels of unconjugated hyperbilirubinemia. A rapidly rising unconjugated bilirubin concentration, or absolute levels (20 mg/dL), puts the infant at risk for **bilirubin encephalopathy, or kernicterus.**

Under these circumstances, bilirubin crosses an immature blood-brain barrier and precipitates in the basal ganglia and other areas of the brain. The consequences range from appreciable neurologic deficits to death. **Treatment options include phototherapy,** which converts bilirubin into water-soluble photoisomers that are excreted directly into bile, and exchange transfusion.

The canalicular mechanisms responsible for bilirubin excretion are also immature at birth, and their maturation may lag behind that of UGT1A1; this can lead to transient conjugated neonatal hyperbilirubinemia, especial lly in infants with hemolysis.

Isolated hyperbilirubinemia: unconjugated bilirubin

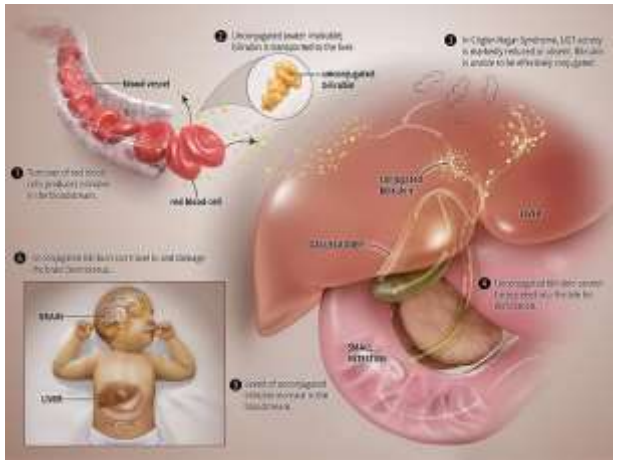
In the absence of hemolysis, the physician should consider a problem with the hepatic uptake or conjugation of bilirubin.

Certain drugs, including rifampicin and probenecid, may cause unconjugated hyperbilirubinemia by diminishing hepatic uptake of bilirubin.

Impaired bilirubin conjugation occurs in three genetic conditions: **Crigler-Najjar syndrome, types I and II, and Gilbert's syndrome.**

Isolated hyperbilirubinemia: unconjugated bilirubin

Crigler-Najjar type I is an exceptionally rare condition found in neonates and characterized by severe jaundice [bilirubin > 342 mol/L **(>20 mg/dL)]** and neurologic impairment due to kernicterus, frequently leading to death in infancy or childhood. These patients have a complete absence of bilirubin UDPGT activity, usually due to mutations in the critical 3' domain of the *UDPGT* gene, and are totally unable to conjugate, hence cannot excrete bilirubin. The only effective treatment is orthotopic liver transplantation. Use of gene therapy and allogeneic hepatocyte infusion are experimental approaches of future promise for this devastating disease.



Isolated hyperbilirubinemia: unconjugated bilirubin

Crigler-Najjar type II is **somewhat more common than type I.** Patients live into adulthood with serum bilirubin levels that range from 103–428 mol/L **(6–25 mg/dL).** In these patients, mutations in the bilirubin *UDPGT* gene cause reduced but not completely absent activity of the enzyme. Bilirubin *UDPGT* activity can be induced by the administration of phenobarbital, which can reduce serum bilirubin levels in these patients. Despite marked jaundice, these patients usually survive into adulthood, although they may be susceptible to kernicterus under the stress of intercurrent illness or surgery.

Isolated hyperbilirubinemia: unconjugated bilirubin

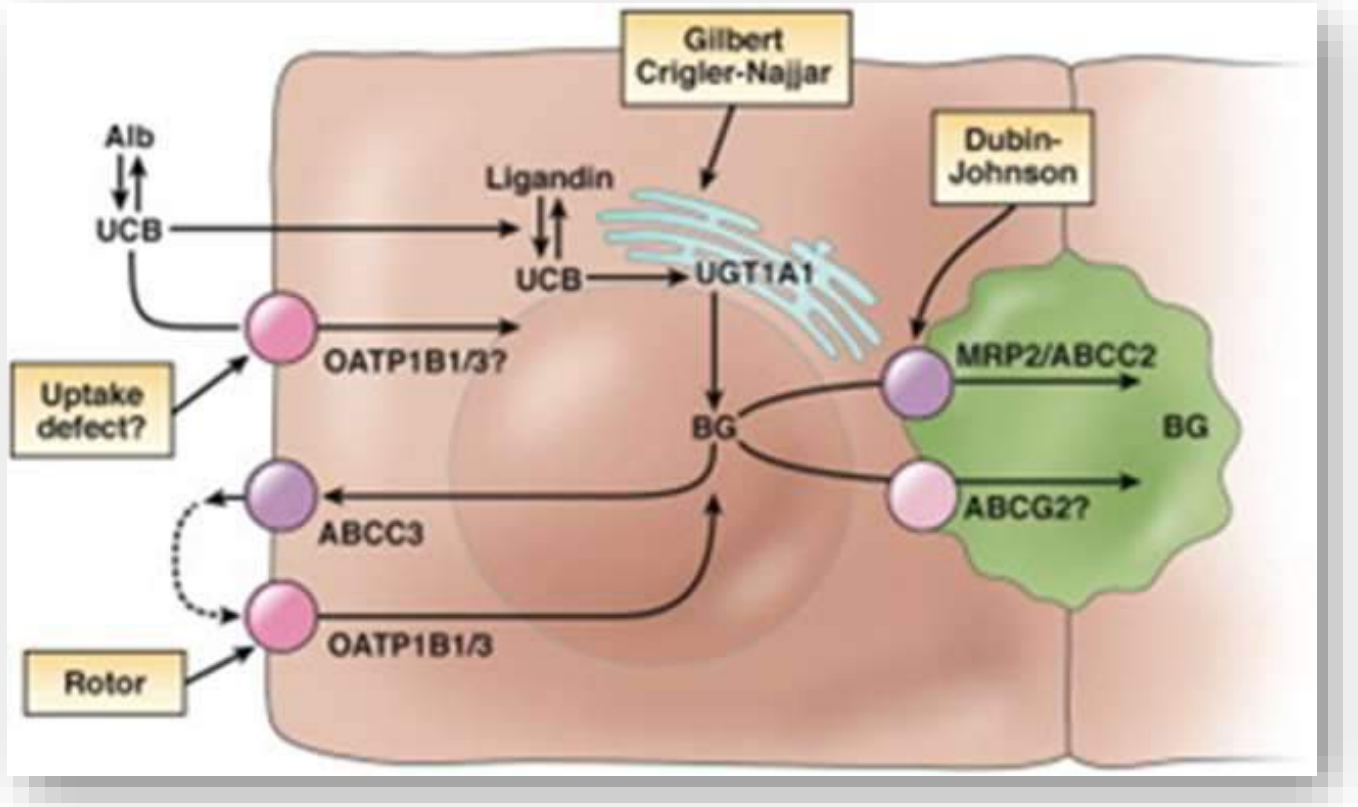
Gilbert's syndrome is also marked by the impaired conjugation of bilirubin due to reduced bilirubin **by bilirubin-UDP-glucuronosyltransferase (UGT1A1) activity.**

- **The reported incidence is 3–7% of the population with males predominating over females by a ratio of 2–7:1.**
- Patients with Gilbert's syndrome have a mild unconjugated hyperbilirubinemia with serum levels almost always **< 6 mg/dL**.
- The serum levels may fluctuate, and jaundice is often identified only during periods of fasting.
- One molecular defect that has been identified in patients with Gilbert's syndrome is in the TATAA element in the 5' promoter region of the bilirubin *UDPGT* gene upstream of exon 1.
- An enhancer polymorphism that lowers transcriptional activity has recently been identified. The decrease in transcription caused by both mutations together may be critical for producing the syndrome. Unlike both Crigler-Najjar syndromes, Gilbert's syndrome is very common.

Isolated hyperbilirubinemia: conjugated bilirubinemia

- Elevated conjugated hyperbilirubinemia is found in two rare inherited conditions: ***Dubin-Johnson syndrome*** and ***Rotor's syndrome***. Patients with both conditions present with **asymptomatic jaundice.**
- **The defect in Dubin-Johnson syndrome is mutations in the gene for multiple drug resistance protein 2 (MRP2).** These patients have altered excretion of bilirubin into the bile ducts.
- **Rotor's syndrome seems to be a problem** with the hepatic storage of bilirubin. Differentiating between these syndromes is possible, but clinically unnecessary, due to their benign nature.

Isolated hyperbilirubinemia: conjugated bilirubinemia



UDPGT bilirubin-UDP-glucuronosyltransferase

TABLE 359-2 PRINCIPAL DIFFERENTIAL CHARACTERISTICS OF INHERITABLE DISORDERS OF BILE CANALICULAR FUNCTION

	DJS	Rotor	PFIC1	BRIC1	PFIC2	BRIC2	PFIC3
Gene	*ABCCA*	*SLCO1B1/SLCO1B3*	*ATP8B1*	*ATP8B1*	*ABCB11*	*ABCB11*	*ABCB4*
Protein	MRP2	OATP1B1/1B3	FIC1	FIC1	BSEP	BSEP	MDR3
Cholestasis	No	No	Yes	Episodic	Yes	Episodic	Yes
Serum γ-GT	Normal	Normal	Normal	Normal	Normal	Normal	↑↑
Serum bile acids	Normal	Normal	↑↑	↑↑ during episodes	↑↑	↑↑ during episodes	↑↑
Clinical features	Mild conjugated hyperbilirubinemia; otherwise normal liver function; dark pigment in liver; characteristic pattern of urinary coproporphyrins	Mild conjugated hyperbilirubinemia; otherwise normal liver function; liver without abnormal pigmentation	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood; decreased phospholipids in bile

Abbreviations: BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt excretory protein; DJS, Dubin-Johnson syndrome; γ-GT, γ-glutamyltransferase; MRP2, multidrug resistance–associated protein 2; OATP1A/1B, organic anion transport proteins 1B1 and 1B3; PFIC, progressive familial intrahepatic cholestasis; ↑↑, increased.

Cholestasis

Cholestasis is defined as a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts.

Therefore, the clinical definition of cholestasis is any condition in which excretion of bile products is impaired and the serum concentrations of conjugated bilirubin and bile acids increase

Cholestatic condition

Conjugated Bilirubin + γGT+ Alc. Phos.

1. Intrahepatic

A. Viral hepatitis

- B and C
- Hepatitis A, Epstein-Barr virus, cytomegalovirus

B. Alcoholic hepatitis

C. Drug toxicity

- 1. Pure cholestasis—anabolic and contraceptive steroids
- 2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
- 3. Chronic cholestasis—chlorpromazine and prochlorperazine

D. Primary biliary cirrhosis

E. Primary sclerosing cholangitis

F. Vanishing bile duct syndrome

1. Chronic rejection of liver transplants
2. Sarcoidosis
3. Drugs

G. Inherited

1. Progressive familial intrahepatic cholestasis
2. Benign recurrent cholestasis

H. Cholestasis of pregnancy

I. Total parenteral nutrition

J. Nonhepatobiliary sepsis

K. Benign postoperative cholestasis

M. Venoocclusive disease

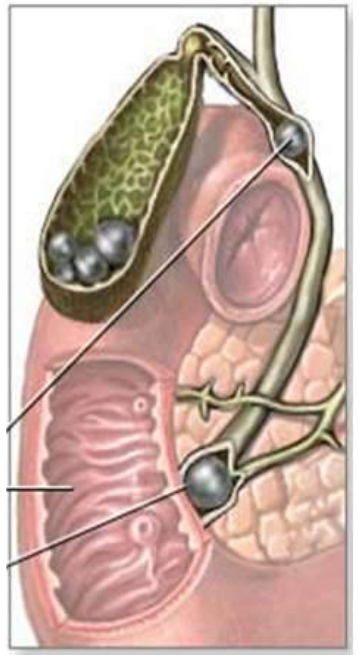
N. Graft-versus-host disease

Cholestatic syndromes
Conjugated Bilirubin + γGT+ Alc. Phosphatase

2. Extrahepatic

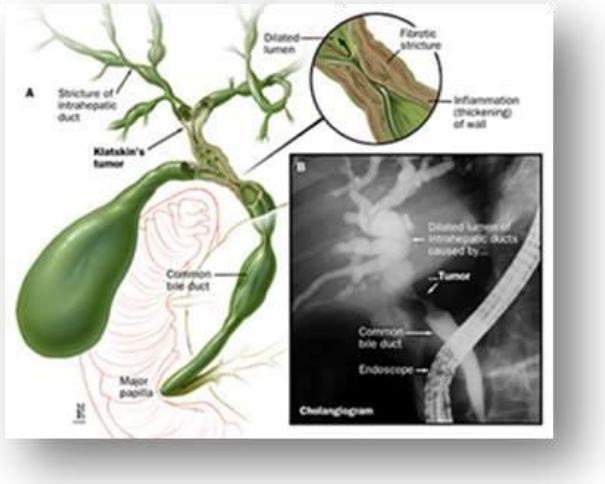
A. Malignant

1. Cholangiocarcinoma
2. Pancreatic cancer
3. Gallbladder cancer
4. Ampullary cancer
5. Malignant involvement of the porta hepatis lymph nodes



B. Benign

1. Choledocholithiasis
2. Postoperative biliary structures
3. Primary sclerosing cholangitis
4. Chronic pancreatitis
5. AIDS cholangiopathy
6. Mirizzi syndrome
7. Parasitic disease (ascariasis)



Clinical approach to cholestasis

What is the main question the physician should evaluate while approaching a patients with cholestasis?

Intrahepatic or extrahepatic

i.e. to establishe wether the bile ducts are dilated or not and the anatomical level of the obstruction

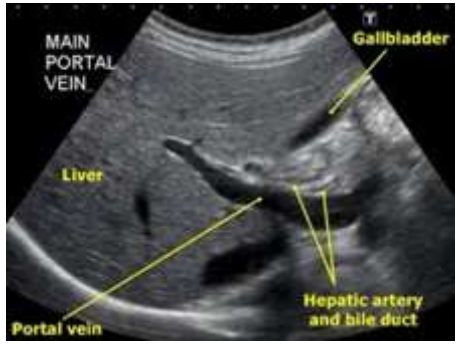
Clinical approach to cholestasis

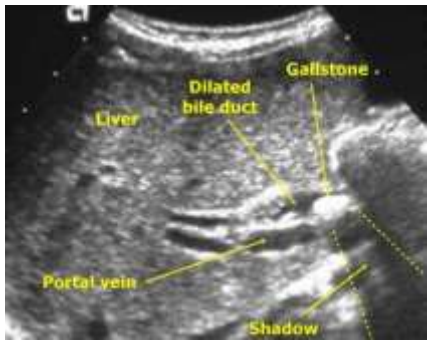
Conjugated Bilirubin + γGT+ Alc. Phosphatase

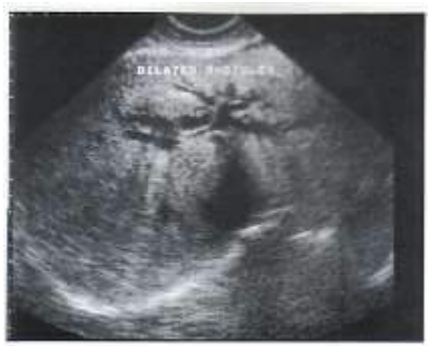
- Clinically distinguishing intrahepatic from extrahepatic cholestasis may be difficult.
- History, physical examination, and **laboratory tests** are often not helpful.

The next appropriate test is an ultrasound

- **The ultrasound is inexpensive**, does not expose the patient to ionizing radiation, and can detect dilation of the intra- and extrahepatic biliary tree with a high degree of sensitivity and specificity.
- The absence of biliary dilatation suggests intrahepatic cholestasis, while the presence of biliary dilatation indicates extrahepatic cholestasis.
- False-negative results occur in patients with partial obstruction of the common bile duct or in patients with cirrhosis or primary sclerosing cholangitis (PSC) where scarring prevents the intrahepatic ducts from dilating.

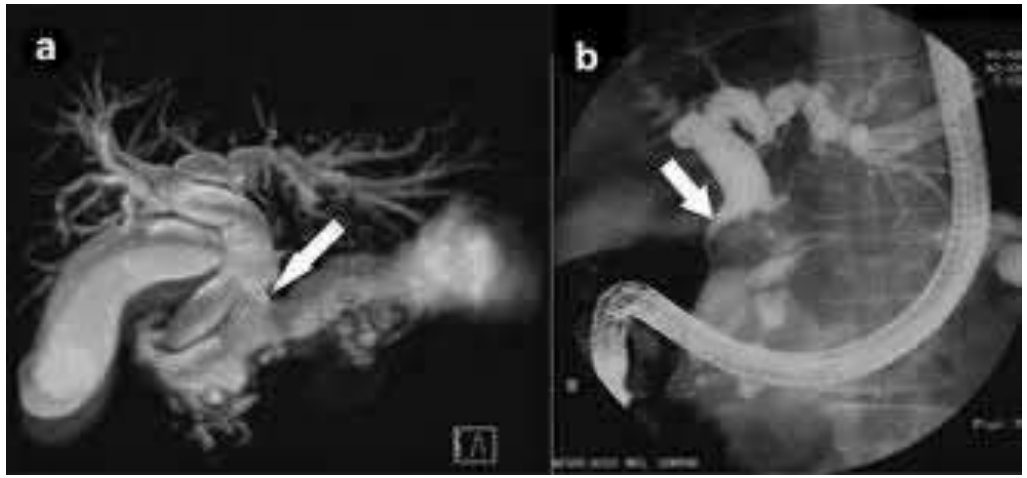






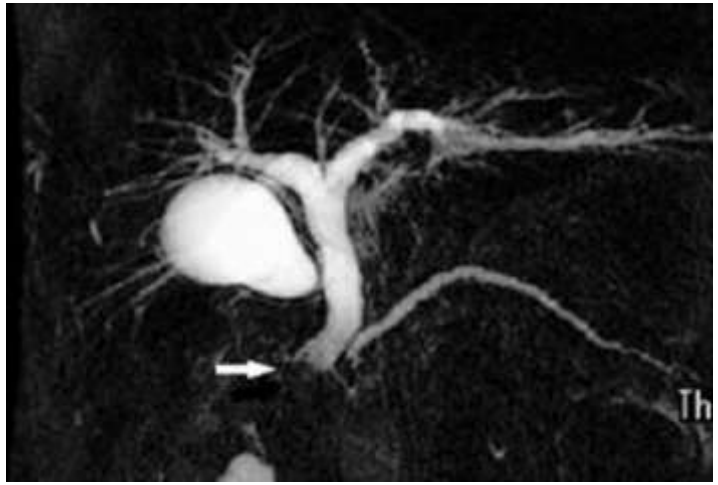
Clinical approach to cholestasis

Although ultrasonography may indicate **extrahepatic cholestasis**, it rarely identifies the site or cause of obstruction. The distal common bile duct is a particularly difficult area to visualize by ultrasound because of overlying bowel gas. Appropriate next tests **include CT, magnetic resonance cholangiography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP).**



MRCP **ERCP**

Intraductal neoplasia



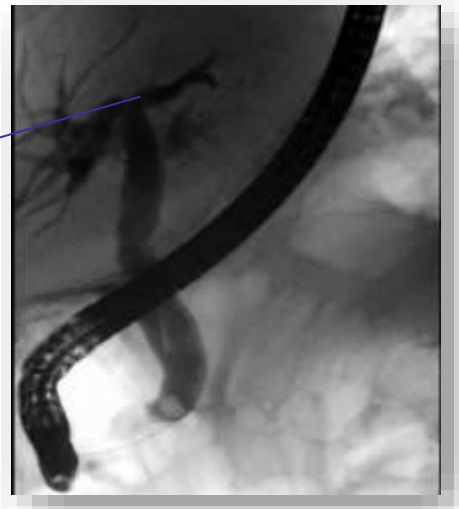
MRCP

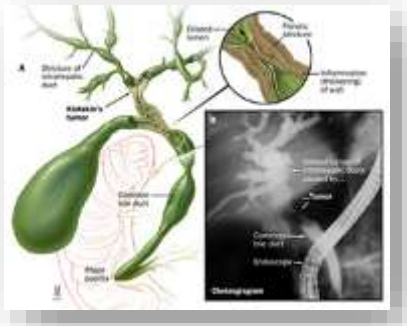
Pancreatic cancer

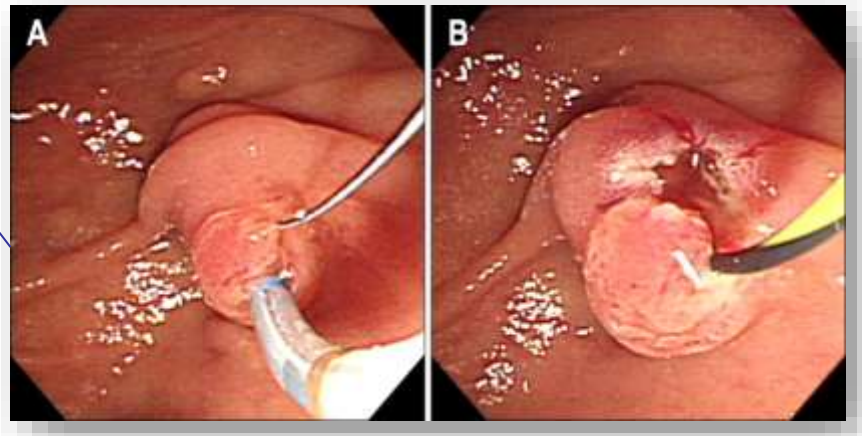
Clinical approach to cholestasis

ERCP- Endoscopic retrograde cholangiography
Endoscopic sphintherotomy

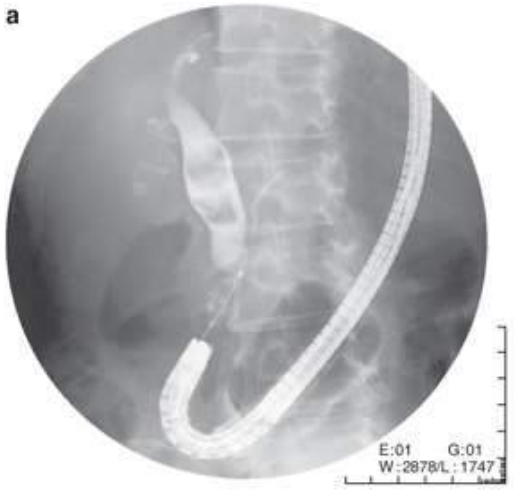
ERCP sphincterotomy and Biliary stone Extraction.mp4

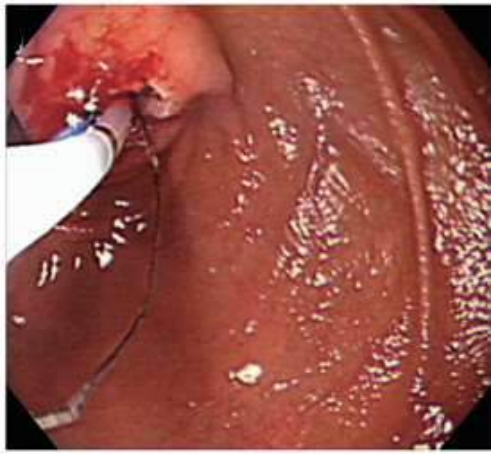


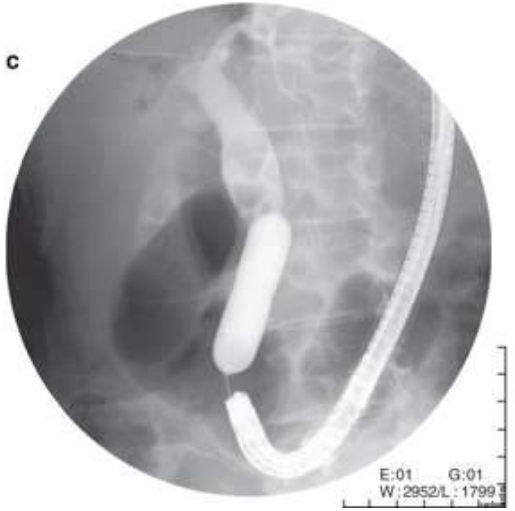


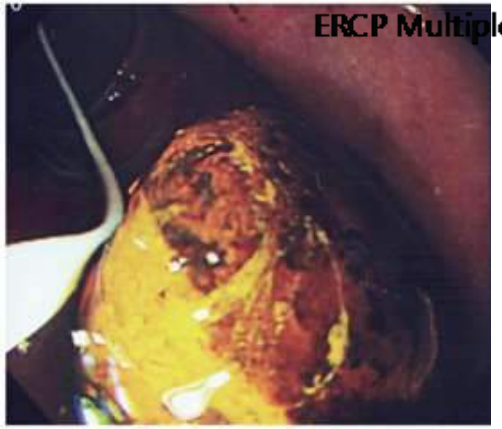


Clinical approach to cholestasis
ERCP



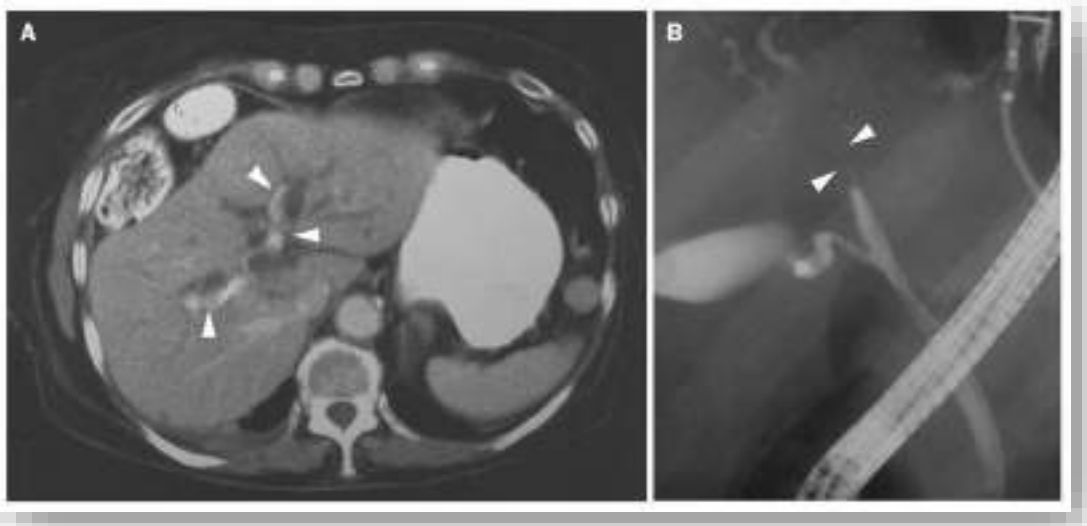


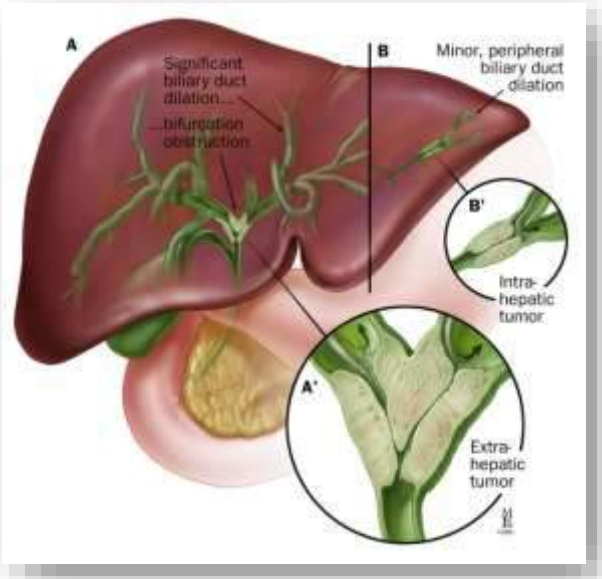


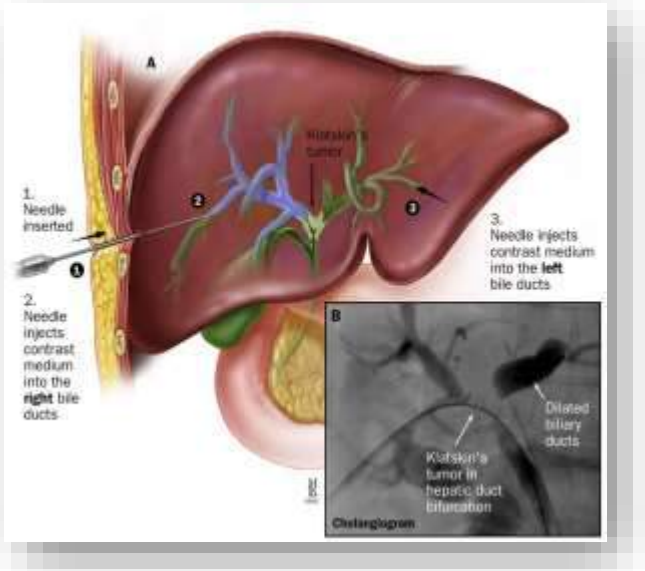


ERCP Multiple CBD stone extraction.mp4

Clinical approach to cholestasis
Percutaneous approach







UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

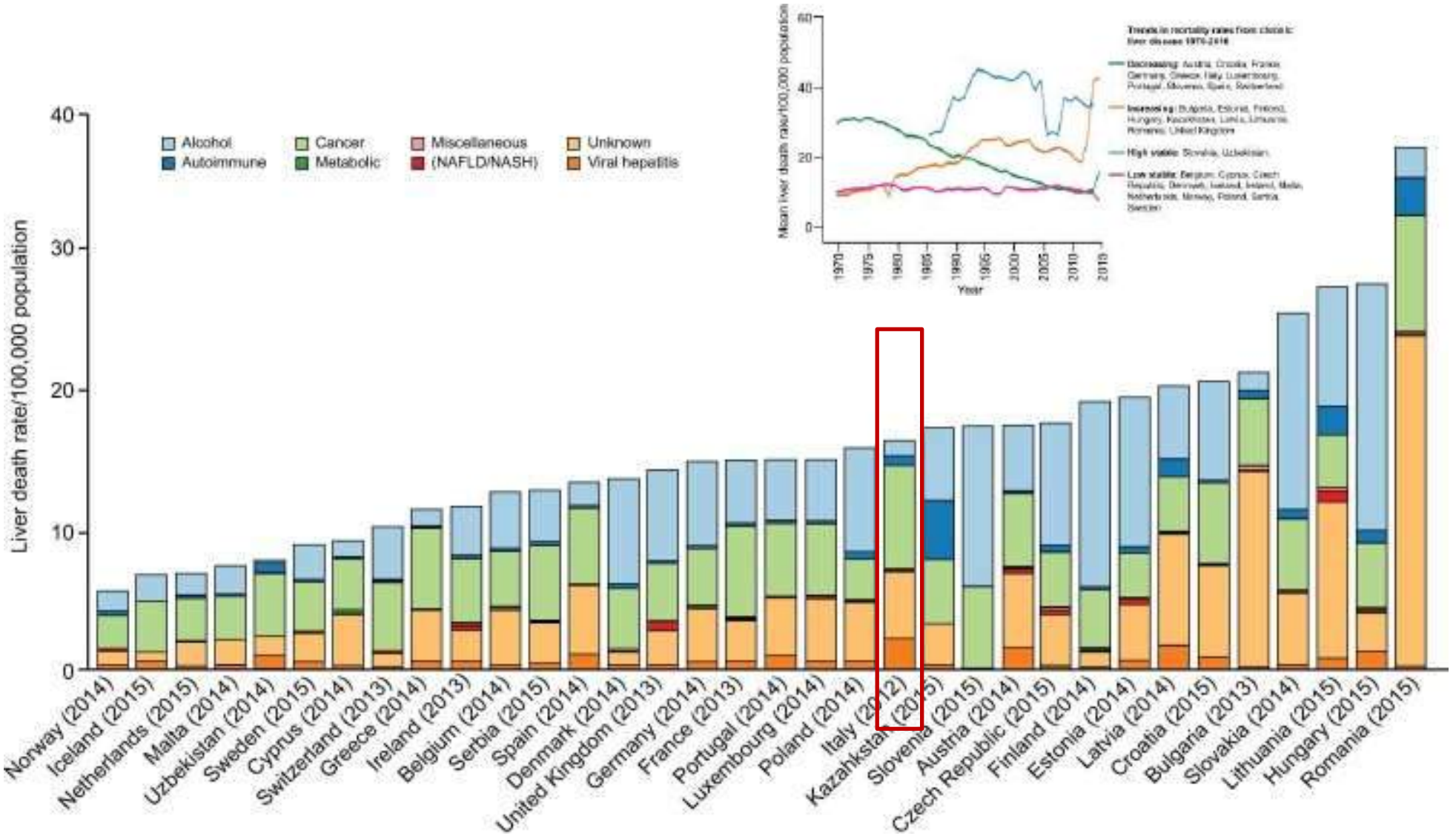
CLMMC AA 2022/23
Patologia sistematica VI
Gastroenterologia

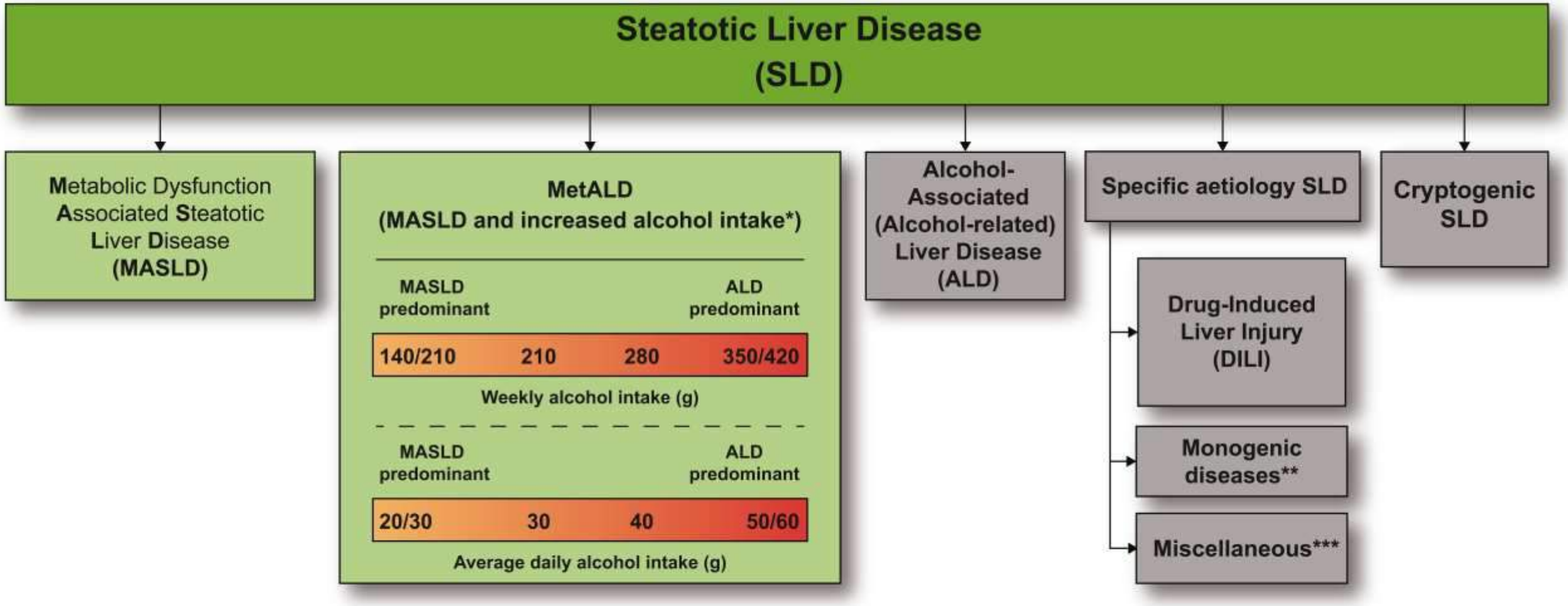
Prof. Stefano Fiorucci
Direttore Scuola di Specializzazione in Malattie Apparato Digerente Università di Perugia

Fatty liver disease

Harrison's Principles of Internal Medicine – 19-20° Ed.

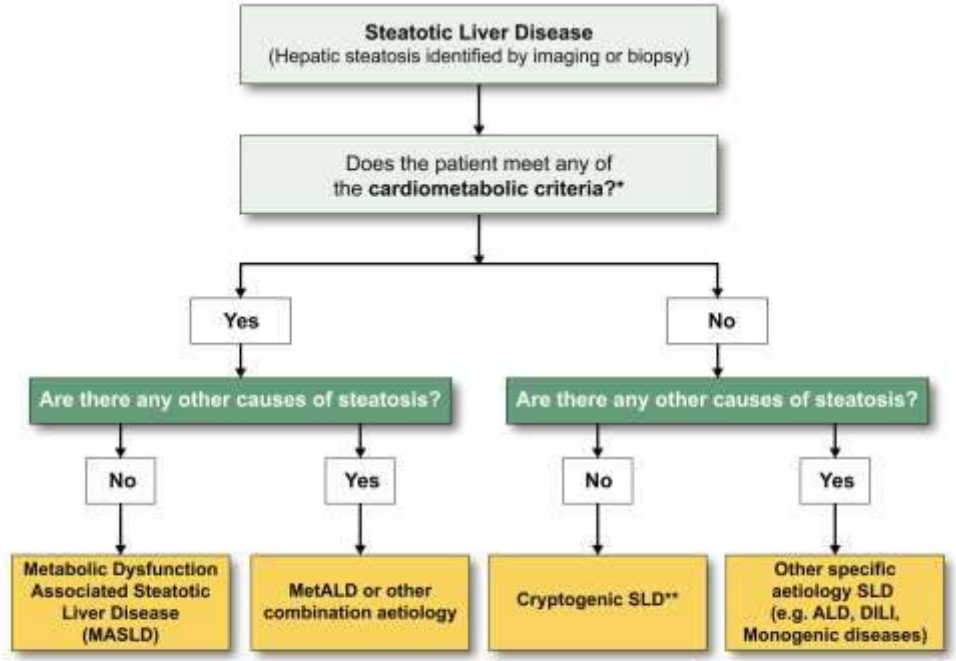
Liver diseases related deaths in Europe 2019





*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

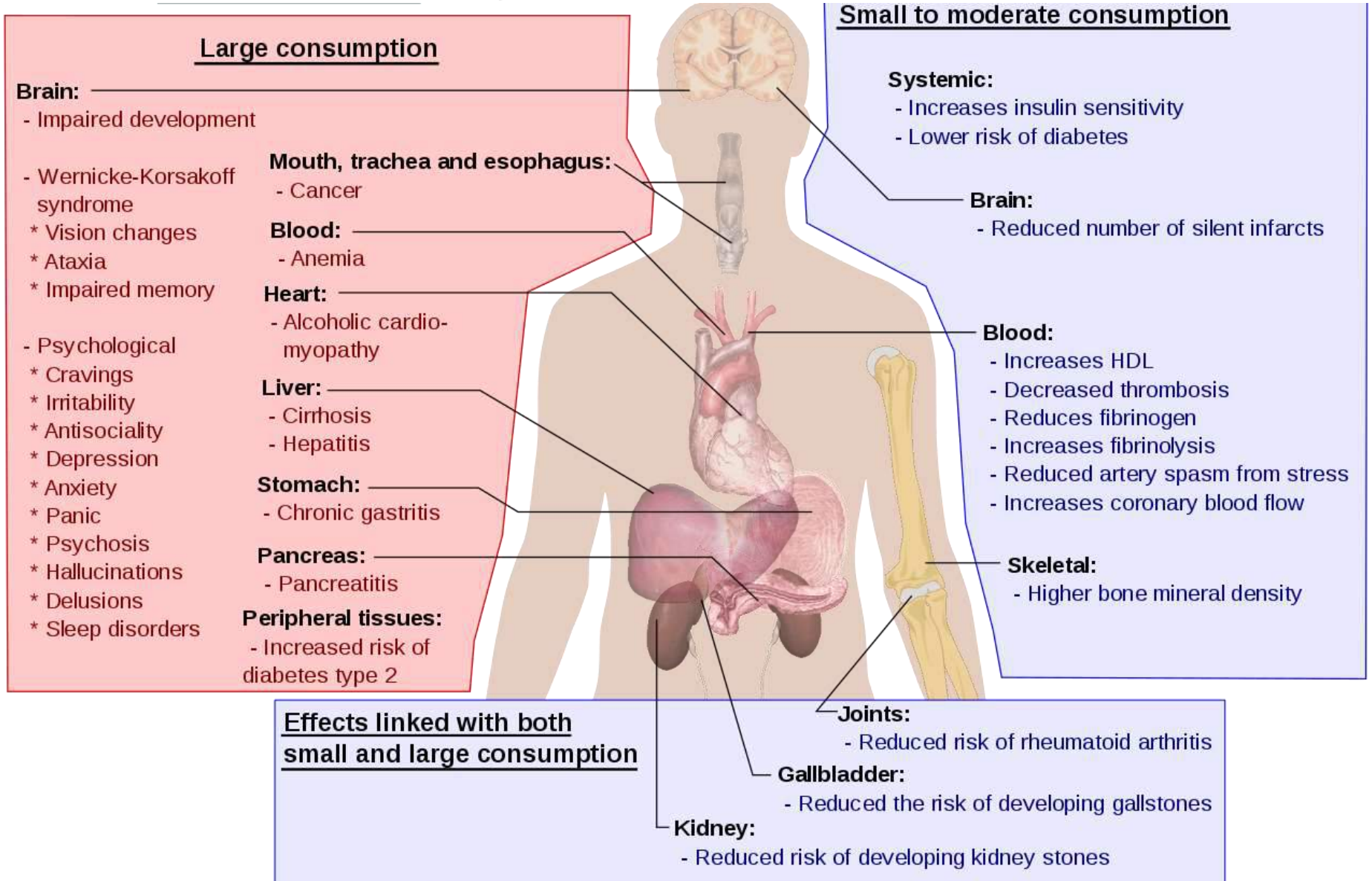
Rinella et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature.
HEPATOLOGY
():10.1097/HEP.0000000000000520. June 24, 2023. | *DOI:* 10.1097/HEP.0000000000000520



***Cardiometabolic criteria**

Adult Criteria	Pediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment	☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Alcoholic liver disease might be part of systemic disease



Alcoholic liver disease

Alcoholic liver disease (ALD), also called alcohol-related liver disease (ARLD), is a term that encompasses the liver manifestations of **alcohol overconsumption**, including:

- **Alcoholic fatty liver disease (ALD)**
- **Alcoholic hepatitis (AH)**
- **Alcoholic steatohepatitis (ASH)**
- **Alcoholic liver fibrosis or**
- **Alcoholic cirrhosis**
- **Alcoholic liver cancer**

EASL -2018

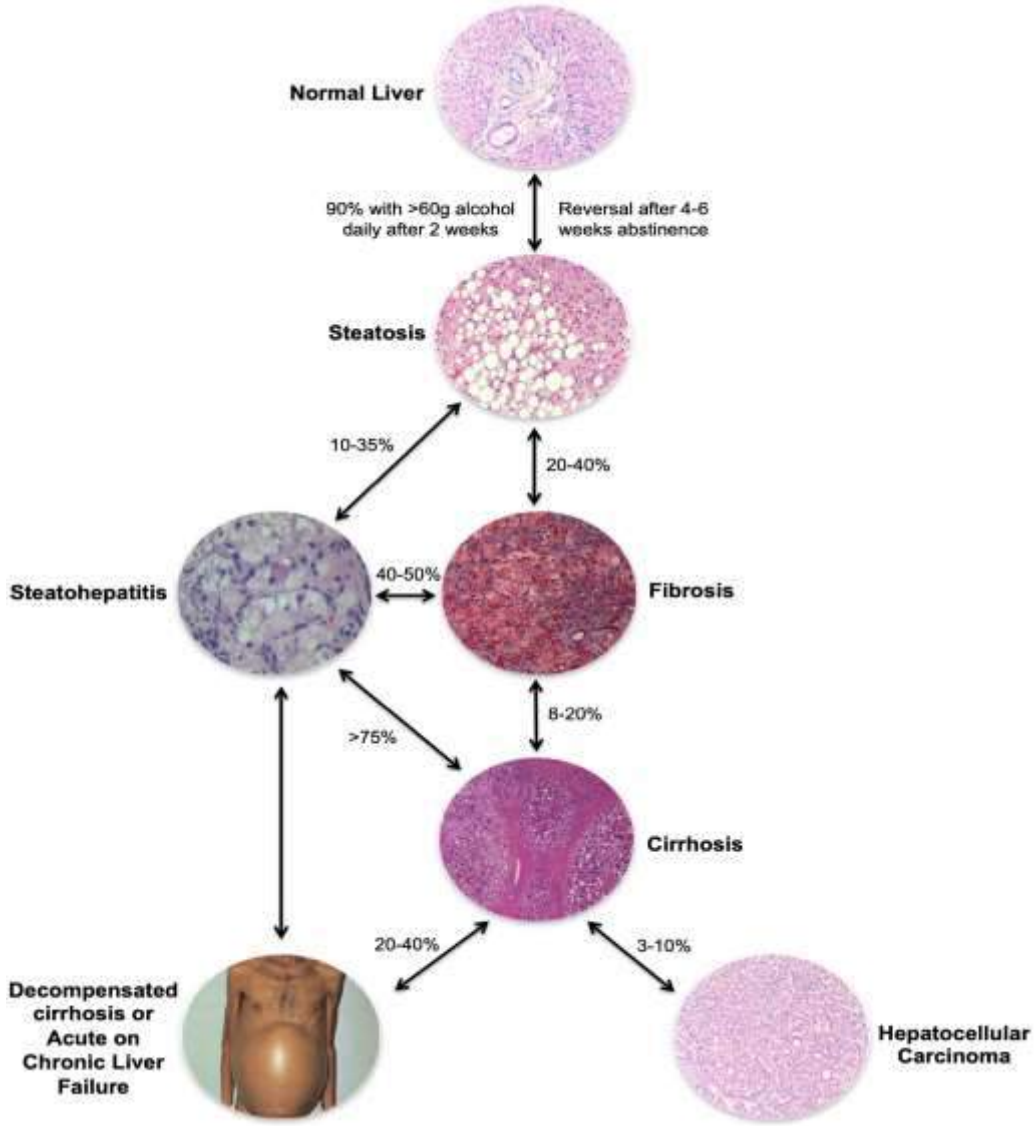
Diagnosis and Treatment of Alcohol-Associated Liver Diseases
Natural history

Although alcohol is considered a direct hepatotoxin, only between 10 and 20% of alcoholics will develop alcoholic hepatitis (comorbid factors such as gender, heredity and immunity)

Fatty liver is present in >90% of binge and chronic drinkers

A much smaller percentage of heavy drinkers will progress to alcoholic steatohepatitis or cirrhosis.

The prognosis of alcoholic liver disease is dismal in most cases;
the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years (acute on chronic)



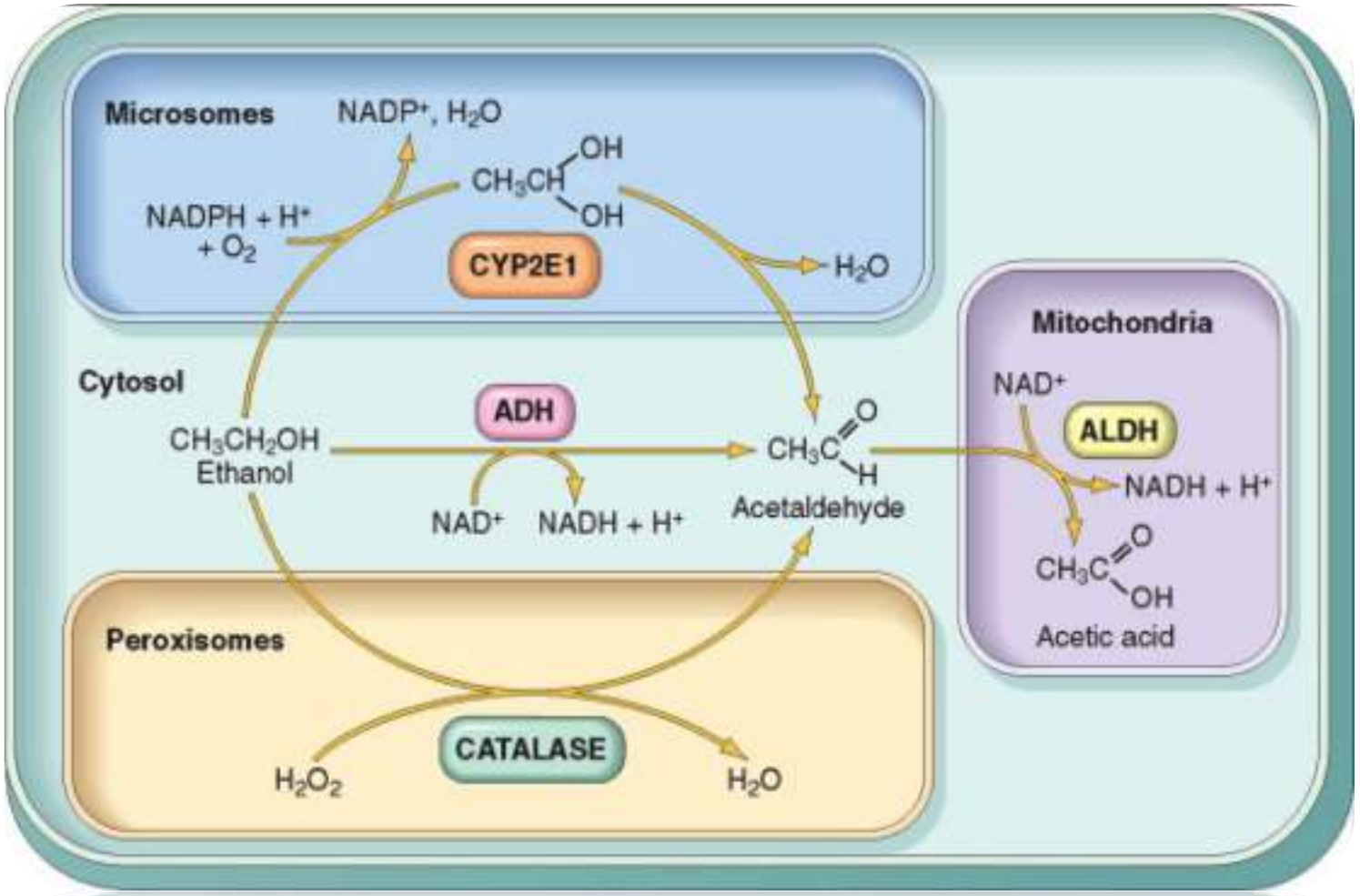
Hepatology, Volume: 71, Issue: 1, Pages: 306-333, First published: 17 July 2019, DOI: (10.1002/hep.30866)

Alcoholic liver disease-pathogenesis

Alcohol is a direct hepatotoxin

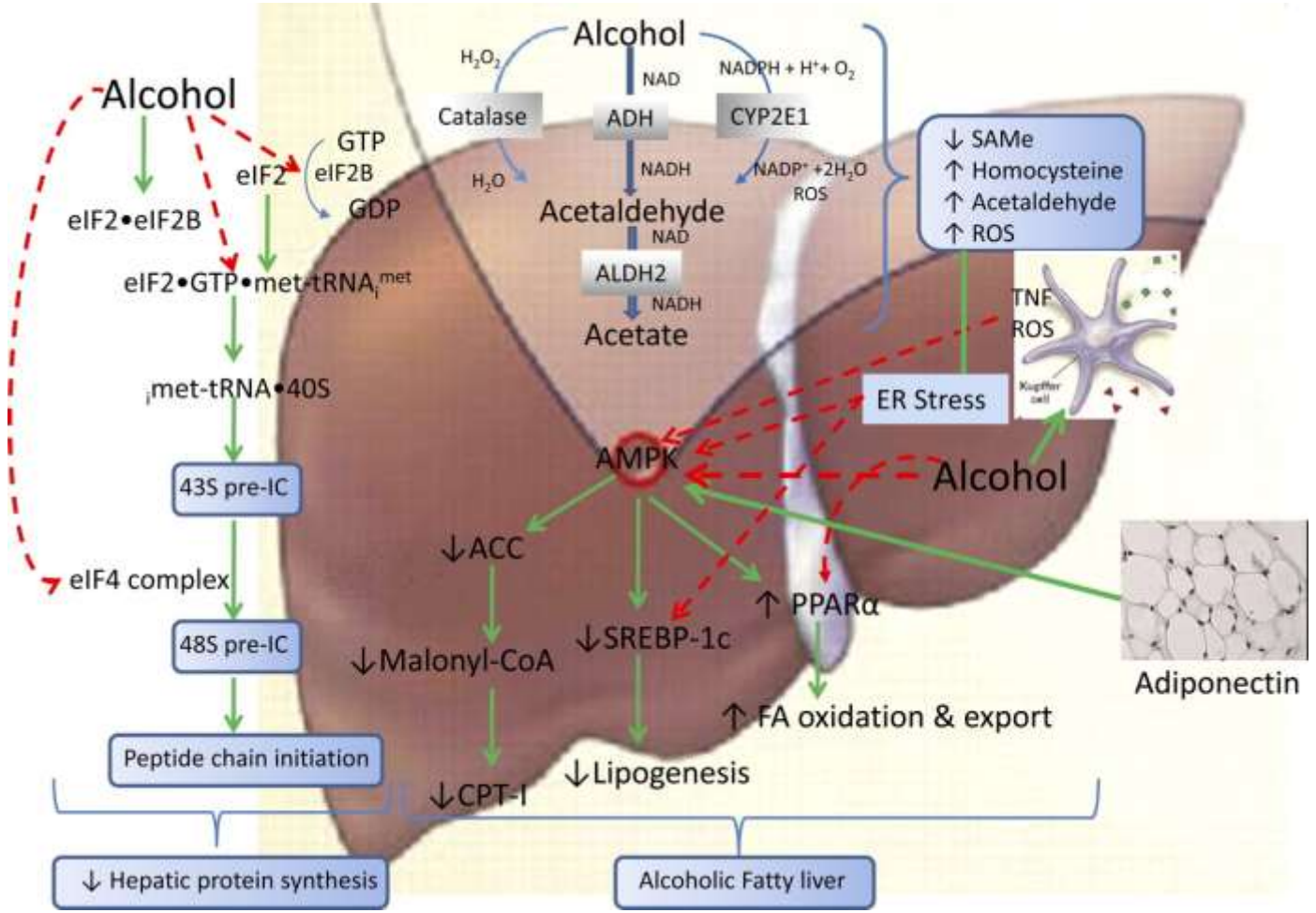
The hepatic metabolism of alcohol initiates a pathogenic process involving production of **toxic protein-aldehyde adducts**, **endotoxins, oxidative stress, immunologic activity, and pro-inflammatory cytokine release**.

Alcohol oxidation to acetaldehyde may occur through cytosolic alcohol dehydrogenase (ADH), cytochrome P-450 (CYP)2E1, or peroxisomal catalase (in that order of importance).



Alcohol oxidation to acetaldehyde may occur through cytosolic alcohol dehydrogenase (ADH), cytochrome P-450 2E1, or peroxisomal catalase (in that order of importance).

AMP kinase (AMPK), a key regulator of metabolism, drives fatty acid (FA) oxidation and export through activation of peroxisome proliferator-activated receptor-α (PPARα); suppresses SREBP-1c, decreasing lipogenesis; and inhibits acetyl-CoA carboxylase (ACC), which through decreased malonyl-CoA levels and carnitine palmitoyltransferase I (CPT I) activity decreases synthesis and increases oxidation of fatty acids.



Patricia E. Molina Am J Physiol Endocrinol Metab 2008;295:E1-E2

Legend to the previous figure

Alcohol oxidation to acetaldehyde may occur through cytosolic **alcohol dehydrogenase (ADH), cytochrome P-450 2E1, or peroxisomal catalase (in that order of importance**). Acetaldehyde is oxidized to acetate by mitochondrial **aldehyde dehydrogenease (ALDH2**). Products of this metabolic pathway result in cellular depletion of S-adenosylmethionine (SAMe) and increased levels of homocysteine, acetaldehyde, and reactive oxygen species (ROS). Together, these factors cause an unfolded-protein response in the endoplasmic reticulum (ER) called ER stress. This activates sterol regulatory element-binding proteins (SREBP-1c and -2c), resulting in triglyceride accumulation. **AMP kinase (AMPK), a key regulator of metabolism, drives fatty acid (FA) oxidation and export through activation of peroxisome proliferator-activated receptor-α (PPARα); suppresses SREBP-1c, decreasing lipogenesis; and inhibits acetyl-CoA carboxylase (ACC), which through decreased malonyl-CoA levels and carnitine palmitoyltransferase I (CPT I) activity decreases synthesis and increases oxidation of fatty acids.**
Activity of AMPK is inhibited by alcohol, ER stress, tumor necrosis factor (TNF), and ROS. Adiponectin released from adipose tissue, which activates AMPK, is in turn suppressed by chronic alcohol consumption. All together, these alcohol-induced effects lead to deranged lipid metabolism and development of fatty liver. Hepatic protein synthesis is suppressed through what appears to be a roadblock in peptide chain initiation. The key step affected by alcohol involves the inability of cycling between the active and inactive forms of the eIF2·eIF2B complex, preventing the formation of the 43S preinitiation complex. Moreover, with chronic alcohol exposure, the defect extends to the ability of the eIF4 complex to effectively regulate the association between the 43S complex and the 5’ cap of mRNA to form the 48S preinitiation complex (pre-IC). Defects in the protein synthetic pathway appear to be the result of a possible dysregulation between the kinase and phosphatase involved in phosphorylation of selected initiation factors. The upstream signals involved are yet to be fully elucidated. Red dotted lines, inhibition of pathway or activation; green solid lines, stimulation or activation of pathway.

Alcoholic liver disease

Risk factors

- **Quantity and duration of alcohol intake are the most important risk factors** involved in the development of **alcoholic liver disease.**
- The roles of beverage type(s), i.e. wine, beer, or spirits, and pattern of drinking are less clear.
- **Progress of the hepatic injury beyond the fatty liver stage seems to require additional risk factors that remain incompletely defined.**
- **Women are more susceptible** to alcoholic liver injury when compared to men. They develop advanced liver disease with substantially less alcohol intake.

Alcoholic liver disease – natural history

Risk threshold of alcohol consumption for liver cirrhosis

An important aspect of public health policy concerning alcohol has been the attempt to establish a safe threshold for consumption.

This revolves primarily around the extent to which moderate alcohol consumption is cardioprotective.

This positive effect of alcohol, if real, can then offset the large array of negative health consequences of even moderate alcohol consumption.

Alcoholic liver disease – natural history

One unit equals 10 ml or 8 g of pure alcohol,

which is around the amount of alcohol the average adult can process in an hour.

Notably, 25% of the population drink more than recommended guidelines (≤14 units/week), with 10% drinking twice as much and 1.4% drinking more than 75 units/week.

The relationship between alcohol consumption and **liver cirrhosis is exponential**; at 20 units/week the relative risk is approximately 3, whereas at 80 units/week it is 30.

There is also a synergy between alcohol intake and obesity; when body mass index (BMI) is >35, the risk of liver disease doubles for any given alcohol intake

In a meta-analysis of **daily consumption** levels in relation to **cirrhosis,** patients taking **50 g of ethanol a day (or 50 unit/week in men and 35 unit/week in women) per 5-10 years increases the risk to develop cirrhosis.**

Risk factors for alcoholic liver disease

325 patients with alcohol-related liver disease

Characterization of metabolic and genetic risk factors

Glucose metabolism

HOMA-IR, HbA1c, P-glucose, diabetes

Lipid metabolism

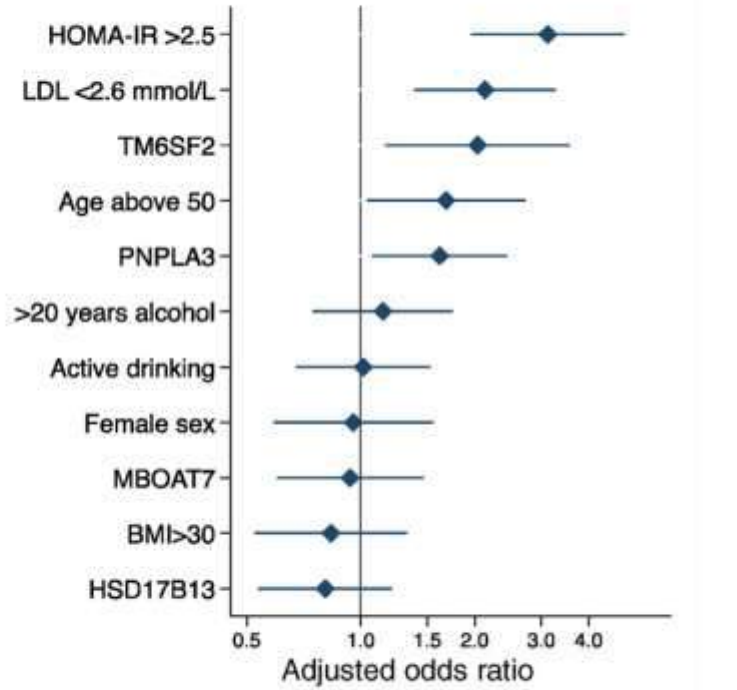
Triglycerides, BMI, Total-, LDL-, HDL-cholesterol

Genetic risk variants

PNPLA3, TM6SF2, MBOAT7, HSD17B13

Histology to assess the severity of liver disease

Insulin resistance (HOMA-IR), LDL cholesterol and genetic susceptibility predicted more severe fibrosis



Clinical Gastroenterology and Hepatology

2020

Alcoholic liver disease and HCV infection

Chronic infection with hepatitis C (HCV) is an important comorbidity in the progression of alcoholic liver disease to cirrhosis in chronic and excessive drinkers.

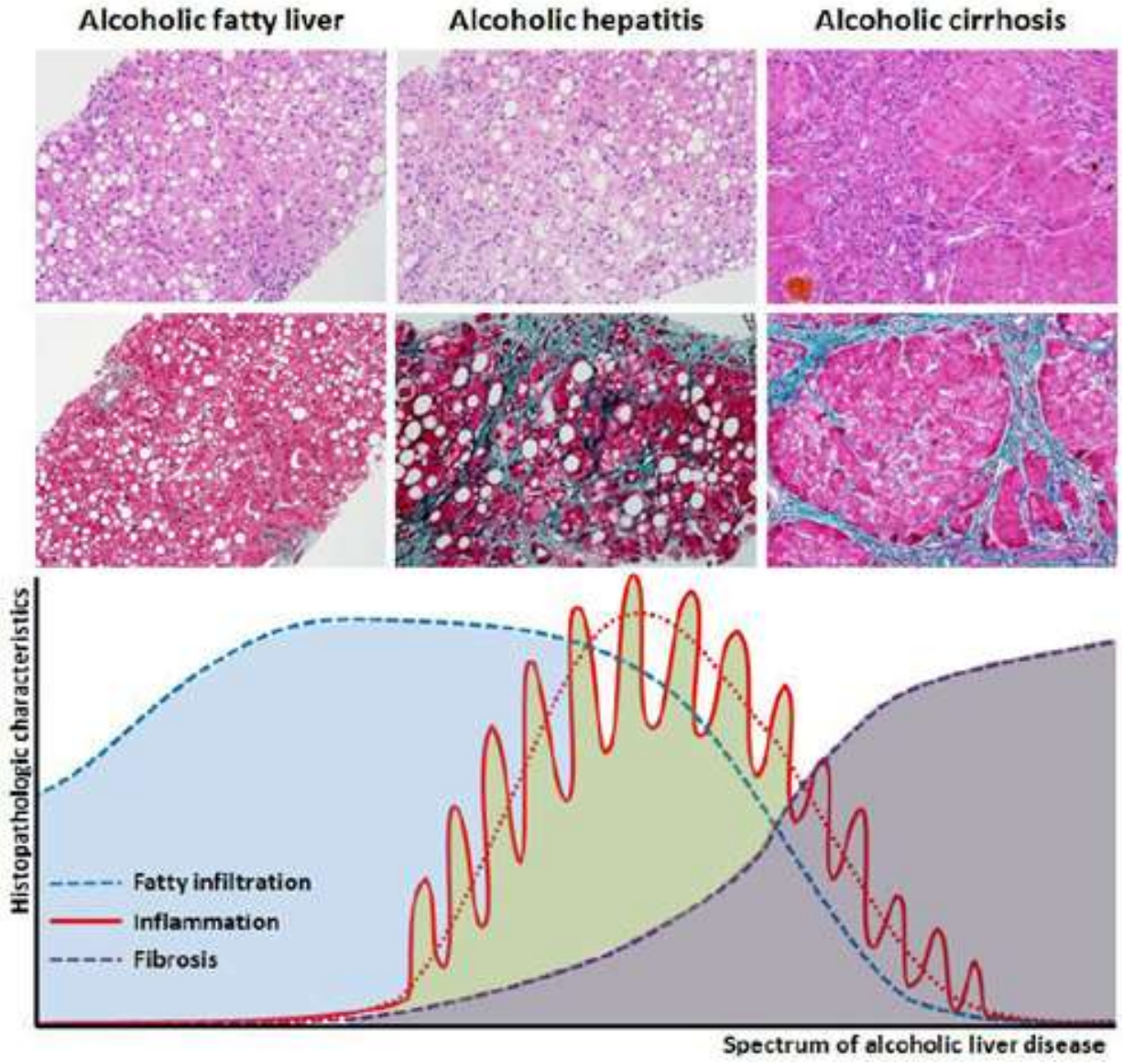
Even moderate alcohol intake increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals.

Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival.

Increased liver iron stores can occur as a consequence of the overlapping injurious processes secondary to alcohol abuse and HCV infection.

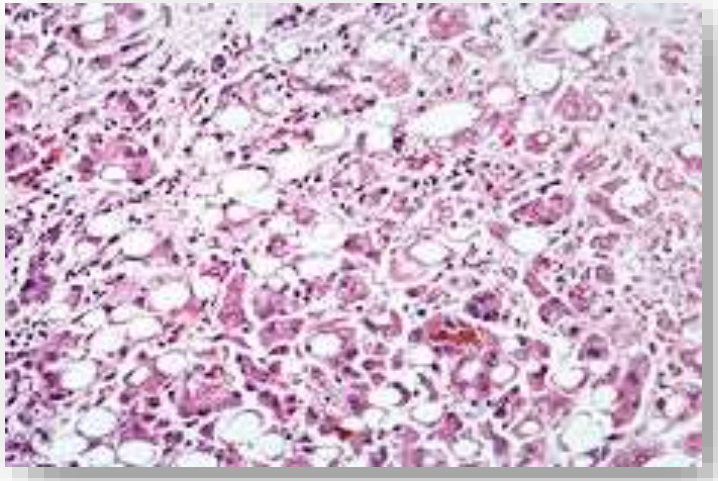
In addition, alcohol intake of >50 g/d by HCV-infected patients decreases the efficacy of interferon-based antiviral therapy.

Alcoholic liver disease-histopathology progression

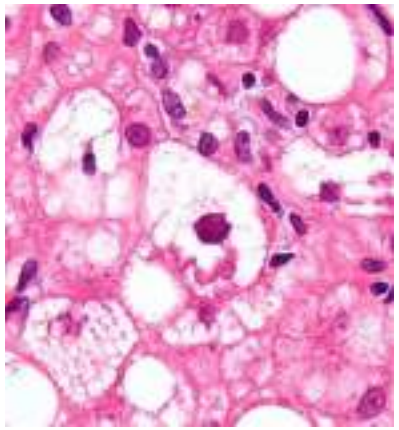


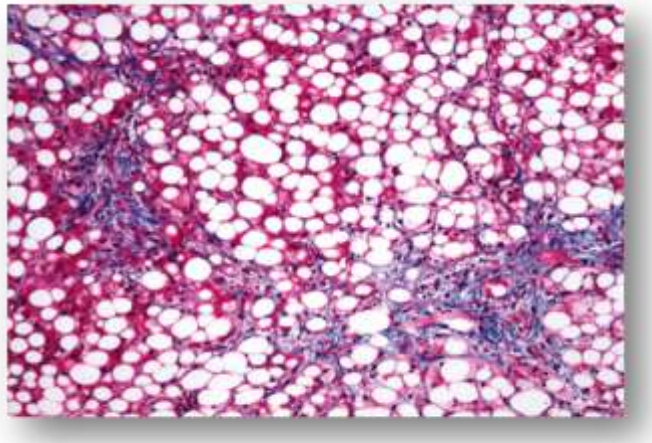
Alcoholic liver disease- histopathology

- **Fatty liver is the initial and most common histologic response to hepatotoxic stimuli, including excessive alcohol ingestion**. The accumulation of fat within the perivenular hepatocytes coincides with the location of **alcohol dehydrogenase**, the major enzyme responsible for alcohol metabolism.
- Continuing alcohol ingestion results in fat accumulation throughout the entire hepatic lobule.
- **Despite extensive fatty change and distortion of the hepatocytes with macrovesicular fat, the cessation of drinking results in normalization of hepatic architecture and fat content within the liver.**



Alcoholic liver disease- histopathology

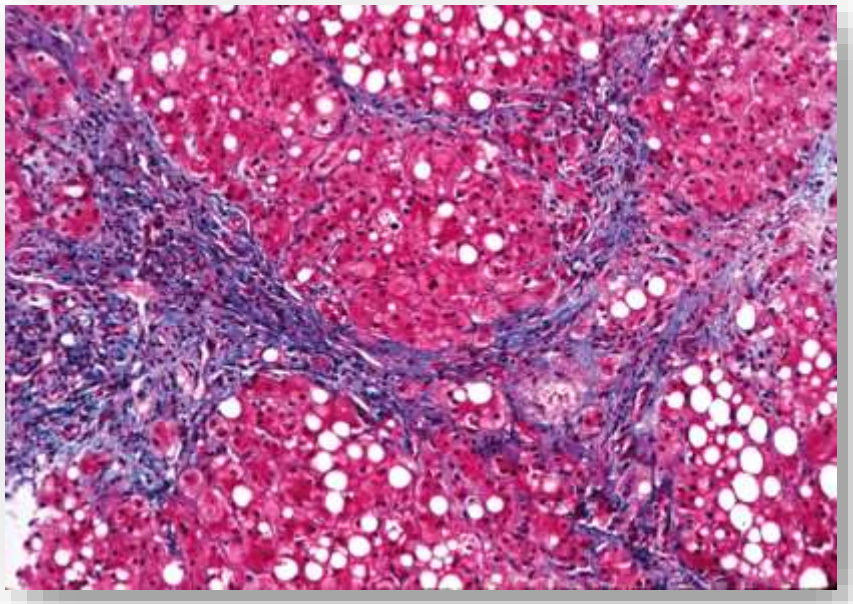


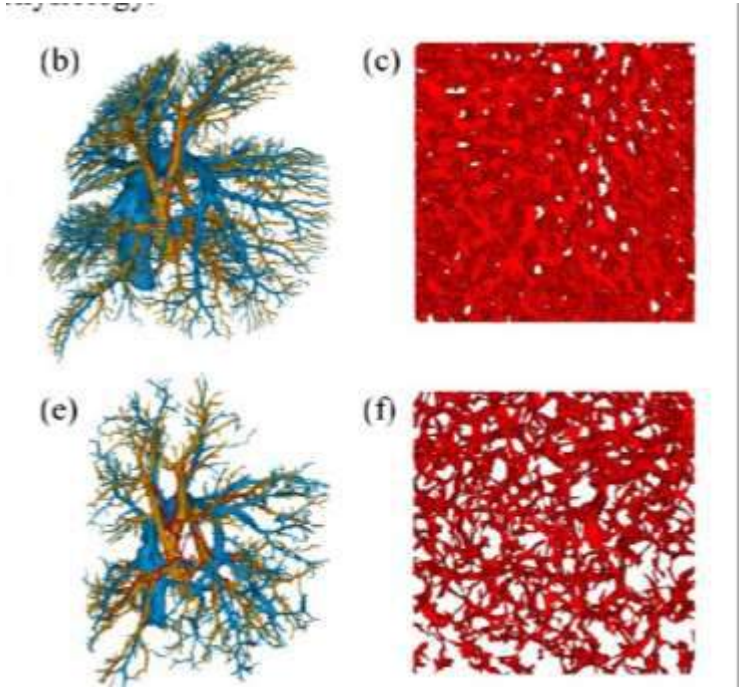


- Alcoholic fatty liver has traditionally been regarded as entirely benign, but similar to the spectrum of nonalcoholic fatty liver disease the appearance of **steatohepatitis and certain pathologic features such as giant mitochondria, perivenular fibrosis, and macrovesicular fat may be associated with progressive liver injury.**
- Mallory bodies are often present in florid cases but are neither specific nor necessary to establishing the diagnosis. Alcoholic hepatitis is thought to be a precursor to the development of cirrhosis. However, like fatty liver, it is potentially reversible with cessation of drinking. Cirrhosis is present in up to 50% of patients with biopsy-proven alcoholic hepatitis and its regression is uncertain, even with abstention

Alcoholic liver disease-histopathology progression

- **The transition between fatty liver and the development of alcoholic hepatitis** is blurred.
- The hallmark of alcoholic hepatitis is hepatocyte injury characterized by ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate, and **fibrosis in the perivenular and perisinusoidal space of Disse.**





Alcoholic liver disease

Clinical presentation

ALD clinical features

Symptoms

- Odor of alcohol on breath*

Nonspecific

- Tiredness
- Abdominal pain
- Day/night reversal (sleepy by day, wakeful at night)
- Peripheral neuropathy
- Weight gain (due to ascites)
- Weight loss (due to loss of proximal muscle mass)
- Confusion (as part of hepatic encephalopathy)
- Loss of sexual drive
- Amenorrhea

Signs

- Skin: Spider angiomata, palmar erythema, leukonychia, ecchymoses
- Eyes: Icteric conjunctivae
- Musculoskeletal: Loss of proximal muscle mass, especially temporal wasting
- Cardiovascular: Systemic hypotension; tachycardia suggests alcohol withdrawal syndrome*
- Abdominal: Ascites, hepatomegaly, splenomegaly, bruits, caput medusa
- Reproductive: Gynecomastia, gonadal atrophy in men
- Neurological:
  - Alcohol withdrawal syndrome*: Fine tremor, psychomotor agitation, transient hallucinations or illusions
  - Hepatic encephalopathy: Coarse flapping tremor (asterixis), altered consciousness
  - Wernicke-Korsakoff syndrome
- Hands: Dupuytren's contracture

*Specific for alcohol; otherwise nonspecific.

Alcoholic liver disease

- The clinical manifestations of alcoholic fatty liver are subtle and characteristically detected as a consequence of the patient's visit for a seemingly unrelated matter.

- Previously unsuspected hepatomegaly is often the only clinical finding. Occasionally, patients with fatty liver will present with right upper quadrant discomfort, tender hepatomegaly, nausea, and jaundice.

- **Differentiation of alcoholic fatty liver from nonalcoholic fatty liver is difficult unless an accurate drinking history is ascertained.**

Alcoholic liver disease

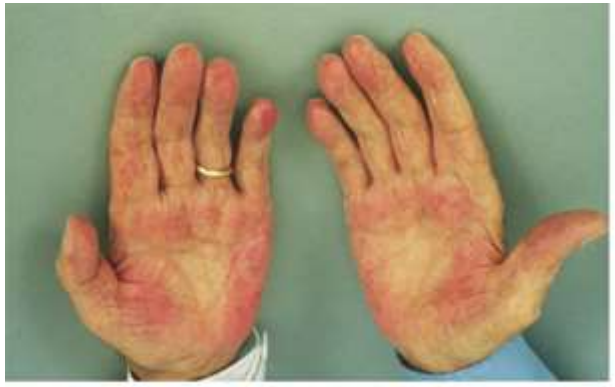
Most patients with moderate forms of ALD are asymptomatic and it can only be detected by appropriate screening methods.

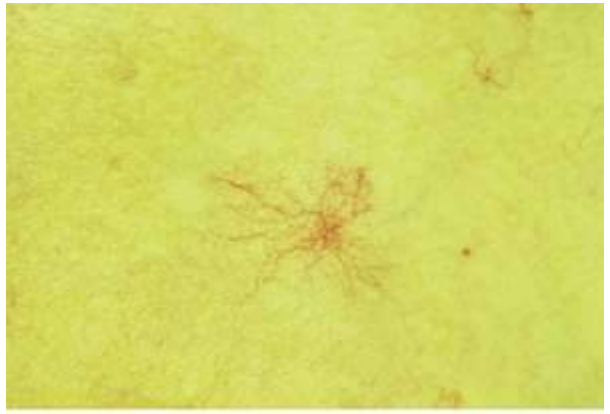
Some patients can show signs suggestive of harmful alcohol drinking such **as bilateral parotid gland hypertrophy**, **muscle wasting, malnutrition, Dupuytren's sign, and signs of symmetric peripheral neuropathy**.

In patients with cirrhosis, most physical findings are not specific of the etiology. However, some signs **such gynecomastia and extensive spider angiomas** may be more frequently seen in those with alcohol as the main cause of liver disease.

Alcoholic liver diseases

- On physical examination, the liver and spleen may be enlarged, with the liver edge being firm and nodular.
- Other frequent findings include scleral icterus, **palmar erythema & spider angiomas parotid gland enlargement, digital clubbing,** muscle wasting, or the development of edema and ascites.
- Men may have **decreased body hair and gynecomastia**
- **Testicular atrophy**, which may be a consequence of hormonal abnormalities or a direct toxic effect of alcohol on the testes.
- In women with advanced alcoholic cirrhosis, menstrual irregularities usually occur, and some women **may be amenorrheic.** These changes are often reversible following cessation of alcohol





Alcoholic liver disease: diagnostic approach

Laboratory Features

- Patients with alcoholic liver disease are often identified through routine screening tests. The typical laboratory abnormalities seen in fatty liver are nonspecific and include:

Direct markers and indirect markers of alcohol consumption

Biomarker	Biological material	Detection window	EtOH amount	Sens.	Spec.	Confounding factors
Breath alcohol	Exhaled air	4–12 hours		97%	93%	Alcohol-containing mouth wash
EtOH	Serum	4–12 hours				
EtG	Urine	Up to 80 hours	>5 g	89%	99%	***Increases*** *results* Accidental contamination of food, mouth wash, alcohol-free beer, etc. with alcohol. UTI ***Decreases*** *results:* Urine dilution deliberately or by diuretics. UTI
EtG	Hair	≤6 months	>20–40 g/d for >3 months	85–92%	87–97%	***Increases*** *results* Seriously impaired renal function EtG containing hair treatment ***Decreases*** *results* Hair treatment: dying, perming, bleaching

Alcoholic liver disease: diagnostic approach

Laboratory Features

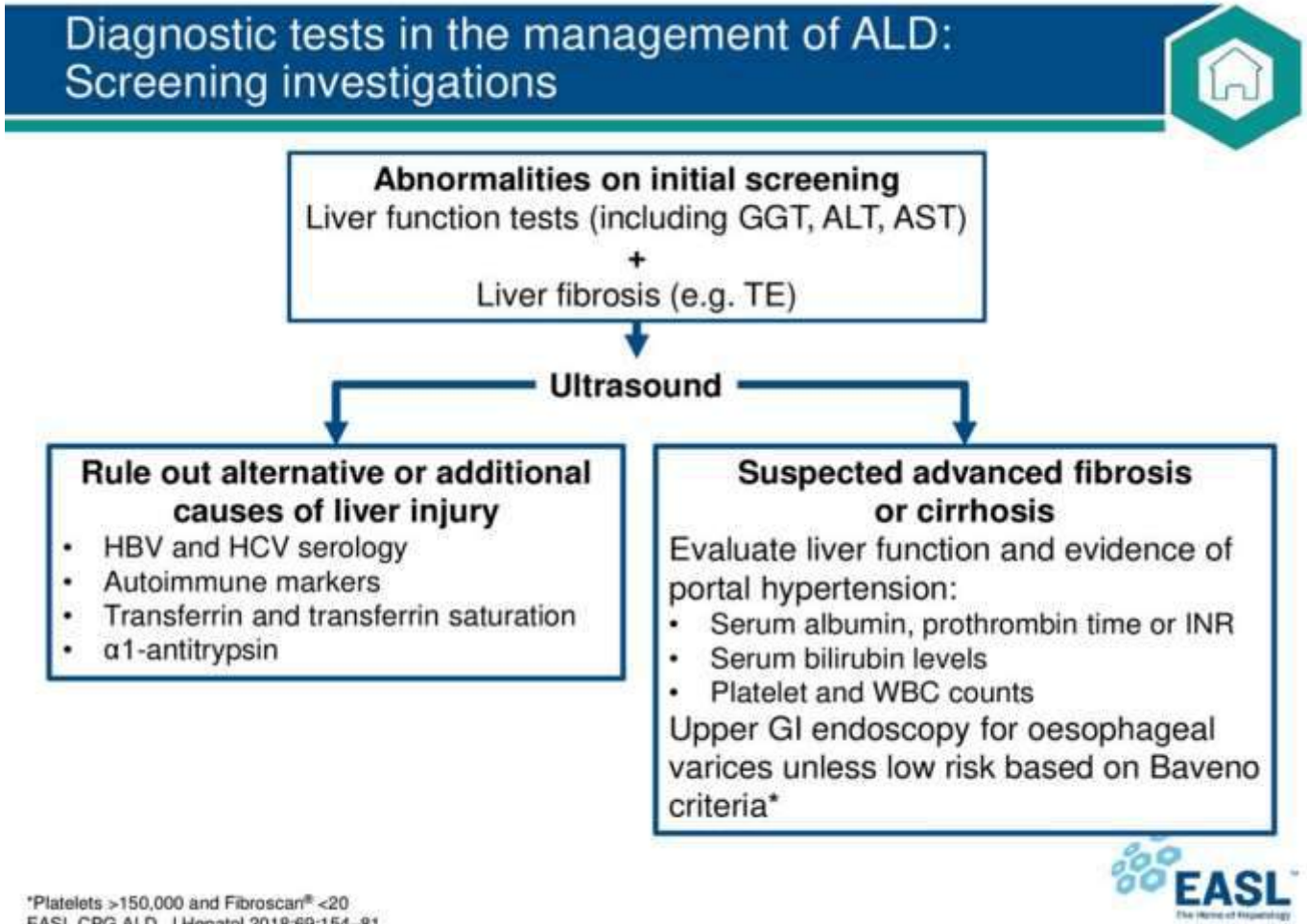
- Patients with alcoholic liver disease are often identified through routine screening tests. The typical laboratory abnormalities seen in fatty liver are nonspecific and include:

Indirect markers and indirect markers of alcohol consumption

Biomarker	Biological material	Detection window	EtOH amount	Sens.	Spec.	Confounding factors
GGT	Serum		Chronic excessive	42–86%	40–84%	Liver disease, BMI, sex, drugs
AST	Serum		Chronic excessive	43–68%	56–95%	Liver and muscle diseases, BMI, drugs
ALT	Serum		Chronic excessive	30–50%	51–92%	Liver disease, BMI, drugs
MCV	Serum		Chronic excessive	24–75%	56–96%	Vitamin B12, folic acid deficiency, haematological diseases
% CDT	Serum	1–2 weeks	50–80 g/d for >1–2 weeks	25–84%	70–98%	Liver cirrhosis/disease, nicotine, transferrin level, weight, sex, pregnancy, rare genetic variations

Alcoholic liver disease: diagnostic approach

Laboratory Features



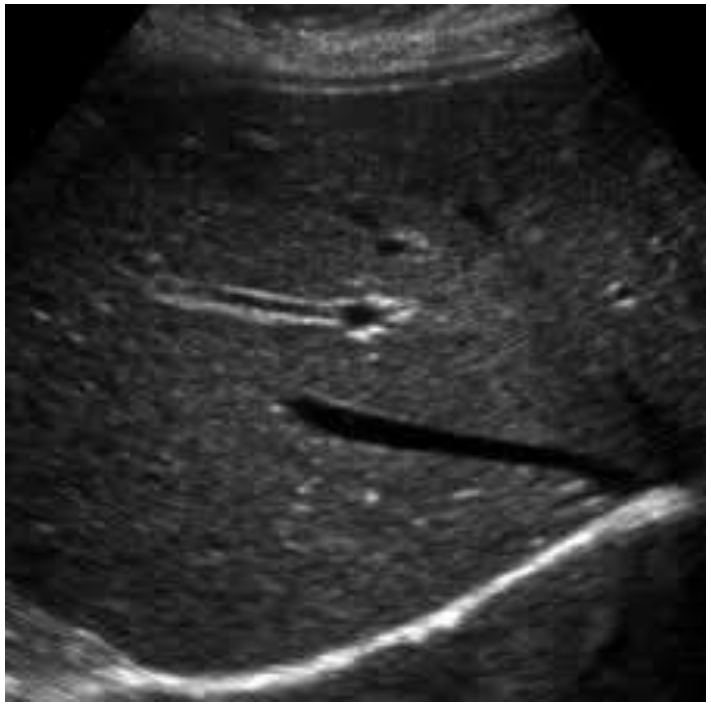
Alcoholic liver disease: diagnostic approach

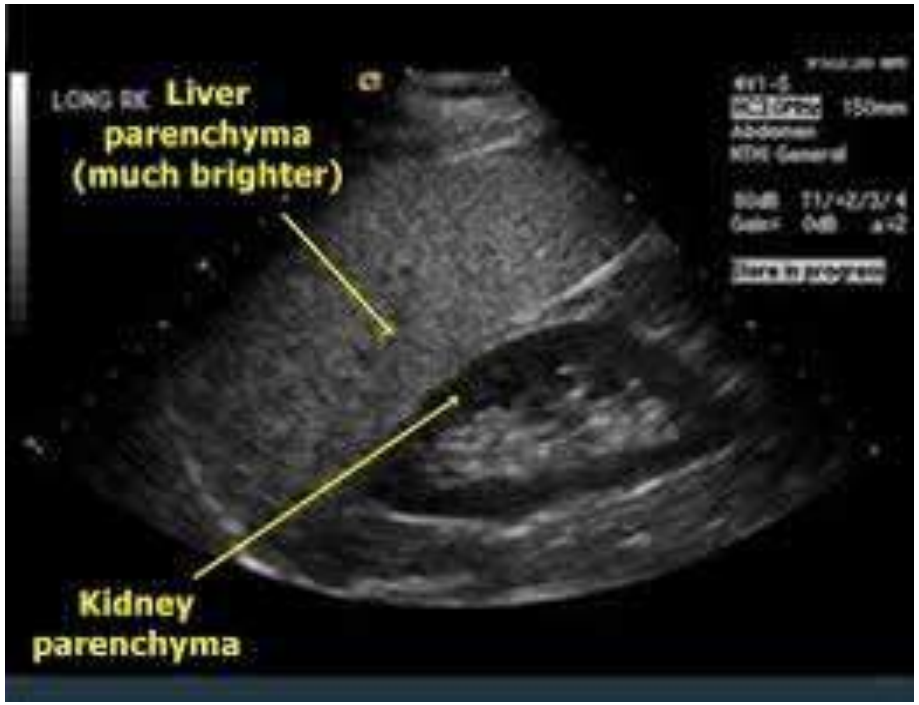
Assesment of steatosis

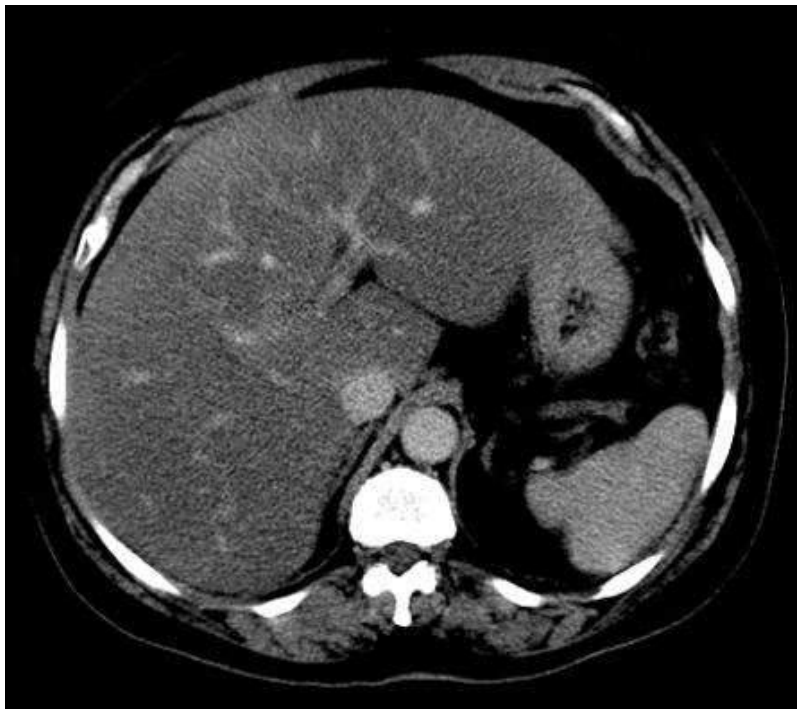
And liver fibrosis

Alcoholic liver disease: diagnostic approach

Ultrasonography is useful in detecting fatty infiltration of the liver and determining liver size. The demonstration by ultrasound of portal vein flow reversal, ascites, and intraabdominal collaterals indicates serious liver injury with less potential for complete reversal of liver disease.







In clinical practice, ultrasonography should be proposed to heavy drinkers as a screening procedure for steatosis .
Ultrasonography can also be useful in detecting signs of advanced stages of ALD such as liver cirrhosis, portal-systemic collaterals and splenomegaly

Alcoholic liver disease: diagnostic approach

- Tests can distinguish mild from severe fibrosis
  - Less well suited to classify intermediate fibrosis stages
- Not helpful in the early diagnosis of ALD

Diagnostic performance of some non-invasive serum fibrosis tests for cirrhosis diagnosis:

Test	Cut-off	F4 prevalence (%)	AUROC (95% CI)	PPV (%)	NPV (%)
Hyaluronic acid	250 µg/L		0.78	35	98
PGAA index*	10	27	0.87 (0.79–0.92)	72	92
FibroTest	≥0.70	31	0.94 (0.90–0.96)	73.4	93.5
	≥0.75	15	0.88 (0.79–0.93)	43.9	92.8
ELF test†	≥10.5	23	0.92 (0.89–0.96)	71	94
Fibrometer	≥0.5	31	0.94 (0.90–0.97)	53.7	98.9
FIB-4	<1.45	31	0.80 (0.72–0.86)	NA	NA
	<1.45	15	0.80 (0.71–0.87)	NA	NA

*PGAA index: combines α2alpha-2-macroglobulin, prothrombin time, serum GGT, serum apolipoprotein A1;
†ELF combines hyaluronic acid (HA), the N-terminal pro-peptide of collagen type III (PIIINP) and tissue inhibitor of metalloproteinase-1 (TIMP-1). The test is validated for diagnosis of ≥F3 fibrosis
EASL CPG ALD. J Hepatol 2018;69:154–81

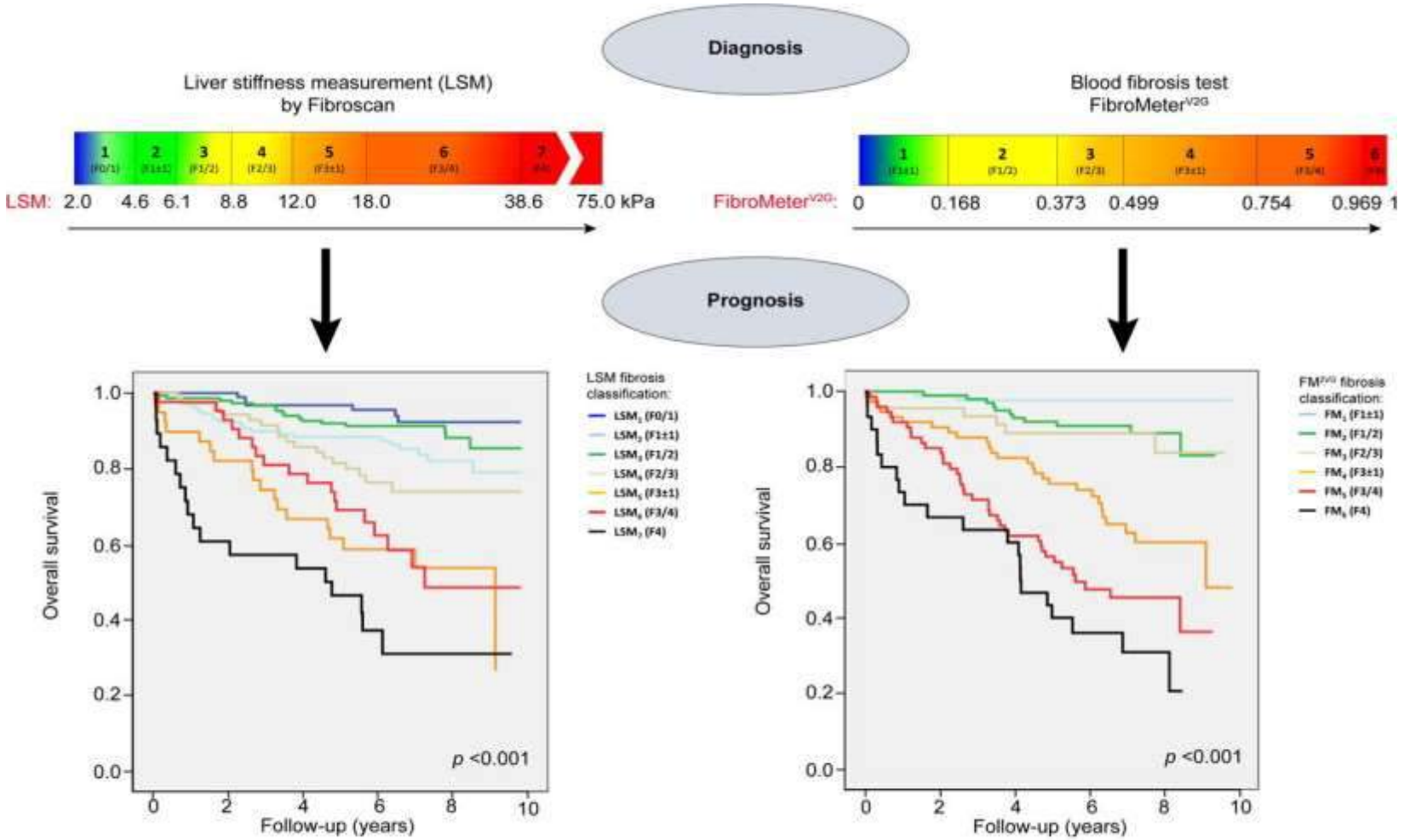
EASL
The Home of Hepatology

Alcoholic liver disease: diagnostic approach

Liver stiffness (LSM)

	F0 to F1	F2	F3	F4
Hepatitis B	2 to 7 kPa	8 to 9 kPa	8 to 11 kPa	18 kPa or higher
Hepatitis C	2 to 7 kPa	8 to 9 kPa	9 to 14 kPa	14 kPa or higher
HIV/HCV Coinfection	2 to 7 kPa	7 to 11 kPa	11 to 14 kPa	14 kPa or higher
Cholestatic Disease	2 to 7 kPa	7 to 9 kPa	9 to 17 kPa	17 kPa or higher
Non-Alcoholic Fatty Liver Disease (NAFLD or NASH)	2 to 7 kPa	7.5 to 10 kPa	10 to 14 kPa	14 kPa or higher
Alcohol Related Disease	2 to 7 kPa	7 to 11 kPa	11 to 19 kPa	19 kPa or higher

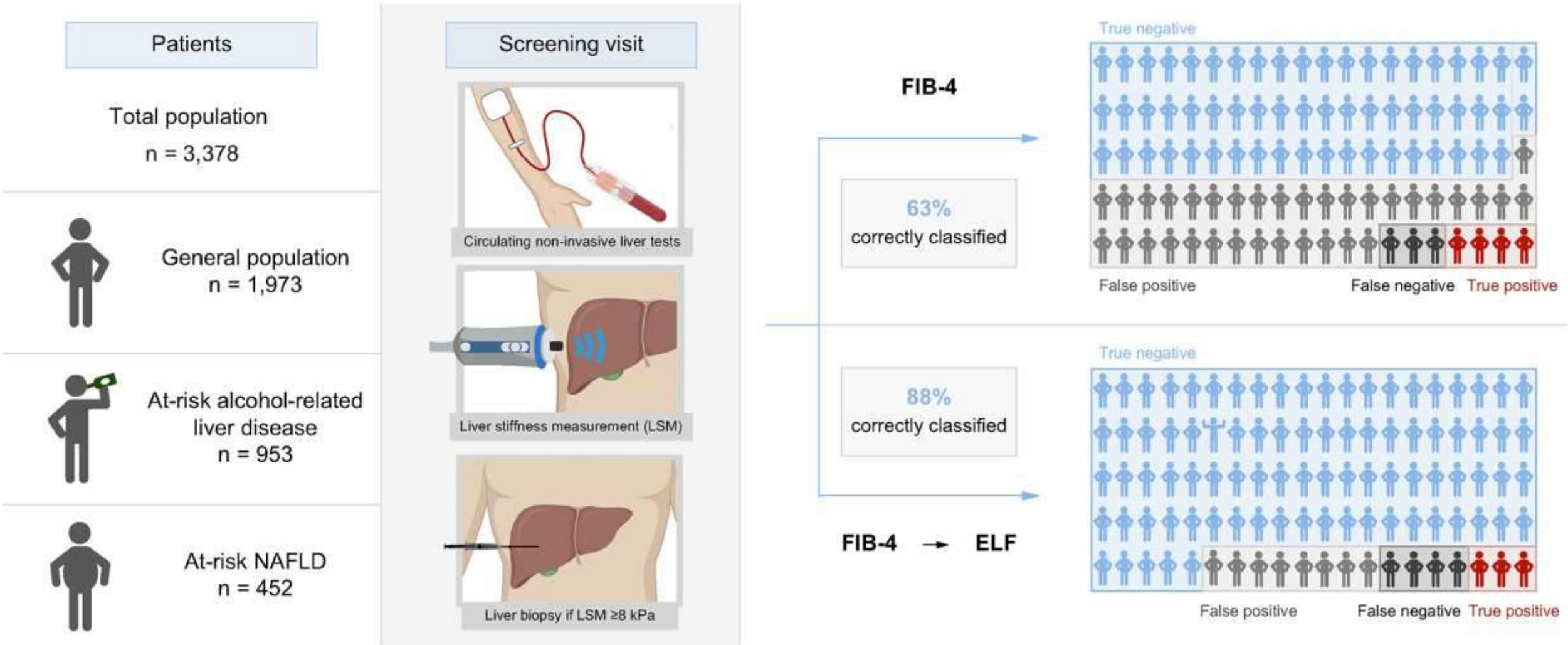
Alcoholic liver disease: diagnostic approach



Non-invasive tests developed for the diagnosis of liver fibrosis are also prognostic markers in NAFLD

Journal of Hepatology 2016 65570-578DOI: (10.1016/j.jhep.2016.04.023)

FIB-4 and ELF


Patients
Total population
n = 3,378
General population
n = 1,973
At-risk alcohol-related liver disease
n = 953
At-risk NAFLD
n = 452
Screening visit
Circulating non-invasive liver tests
Liver stiffness measurement (LSM)
Liver biopsy if LSM ≥8 kPa
FIB-4
63%
correctly classified
True negative
False positive
False negative
True positive
88%
correctly classified
FIB-4 → ELF
True negative
False positive
False negative
True positive

Alcoholic hepatitis

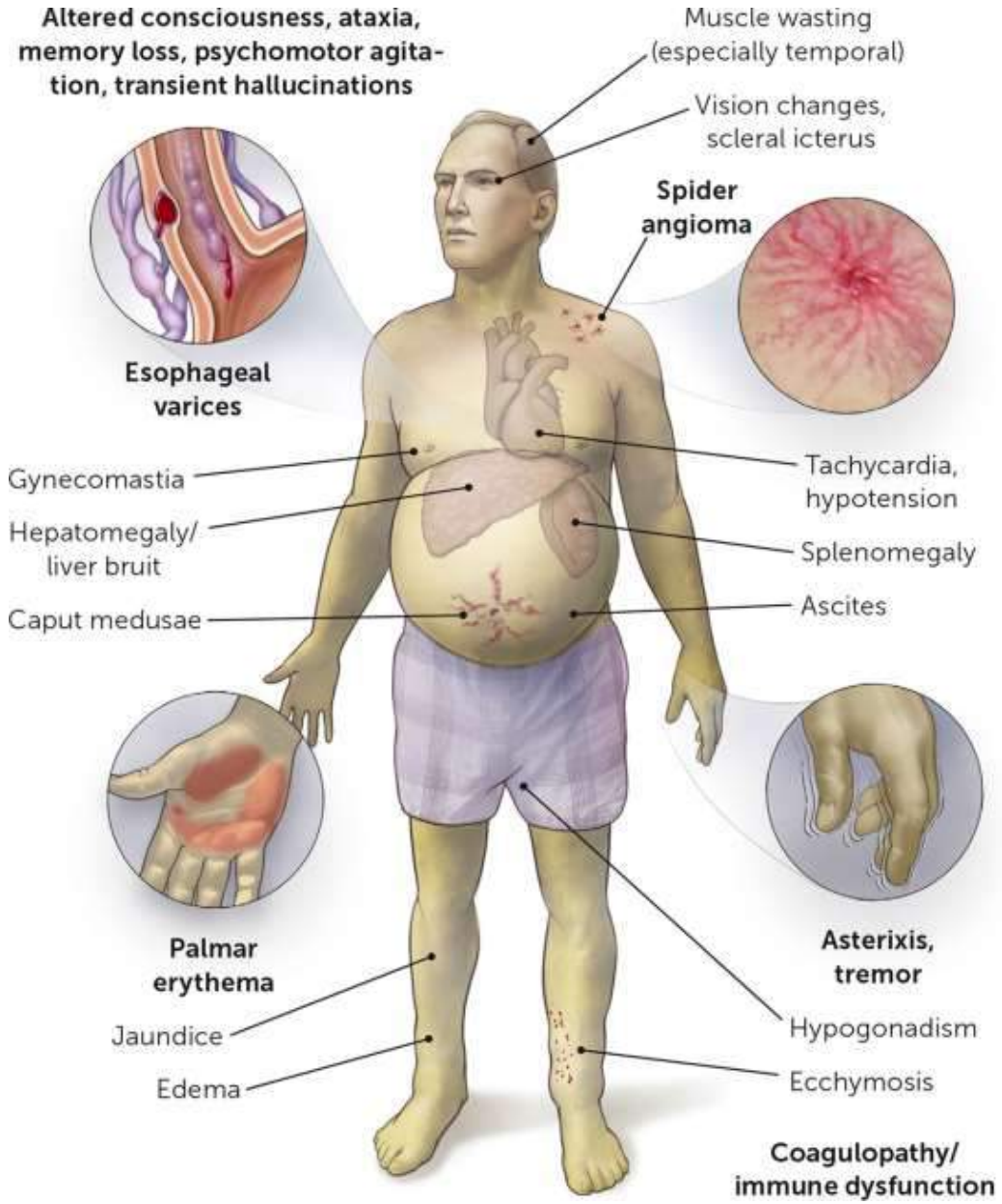
Alcoholic hepatitis (acute alcoholic hepatitis) and acute on chronic

Alcoholic hepatitis is a clinical syndrome **defined by the recent onset of jaundice and/or liver decompensation (i.e. ascites) in a patient with chronic alcohol abuse .**

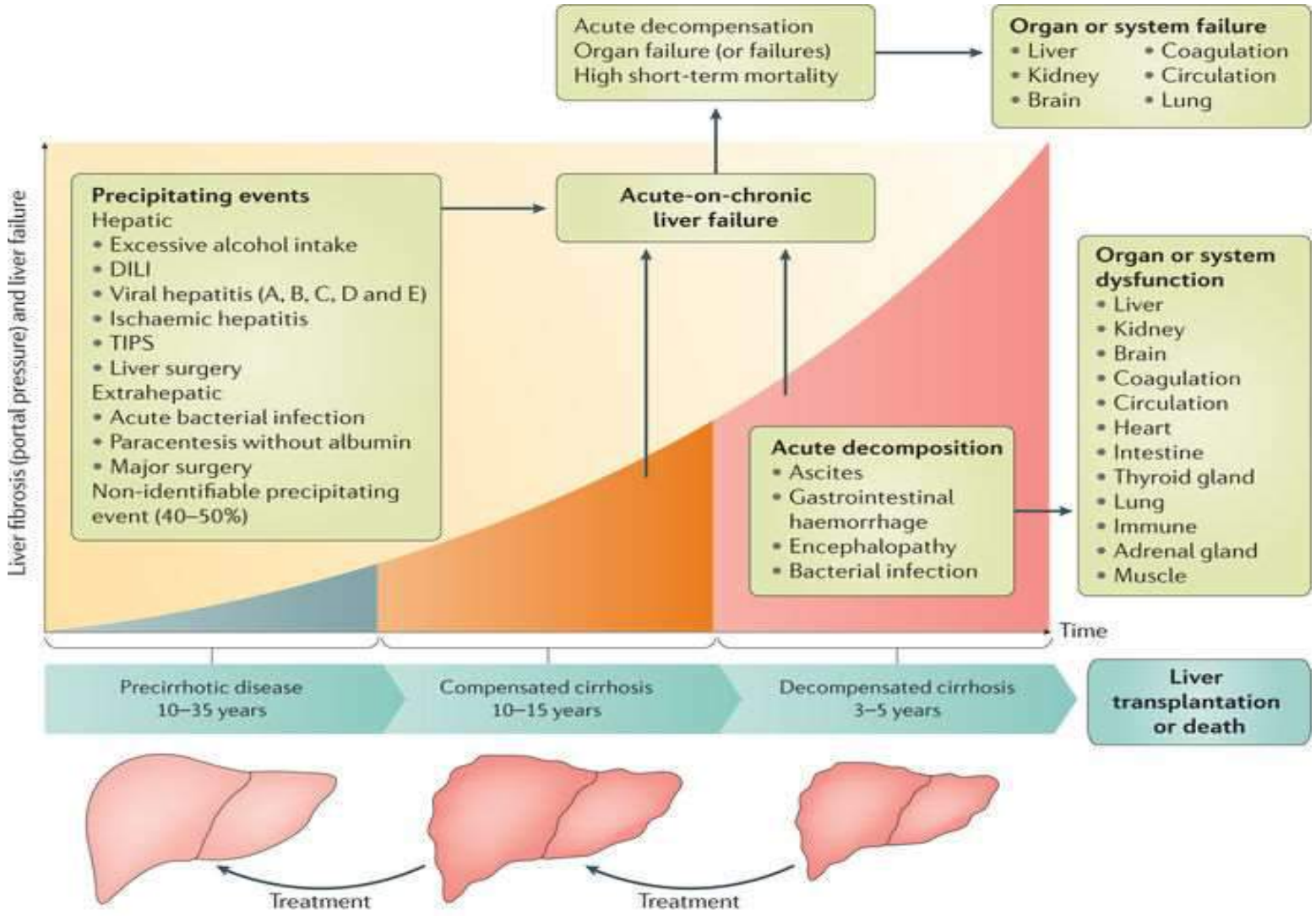
Historically, it was referred to as “acute alcoholic hepatitis”.

Although the clinical presentation may present abruptly, the term “acute” is not recommended, since it is an exacerbation of an underlying chronic liver disease and usually follows an extended course.

Alcoholic liver disease

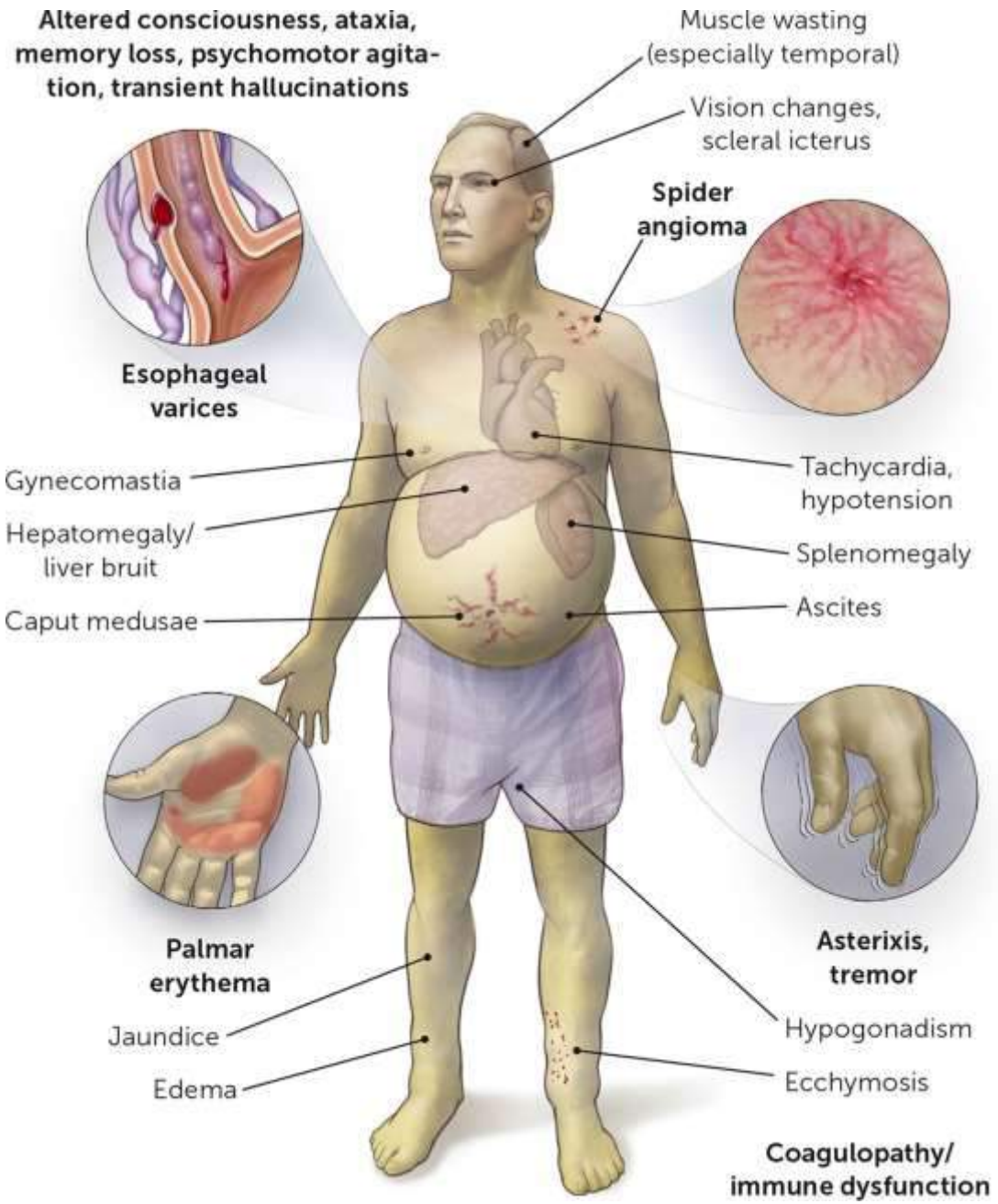


Alcoholic hepatitis



Nature Reviews | Disease Primers

Alcoholic hepatitis

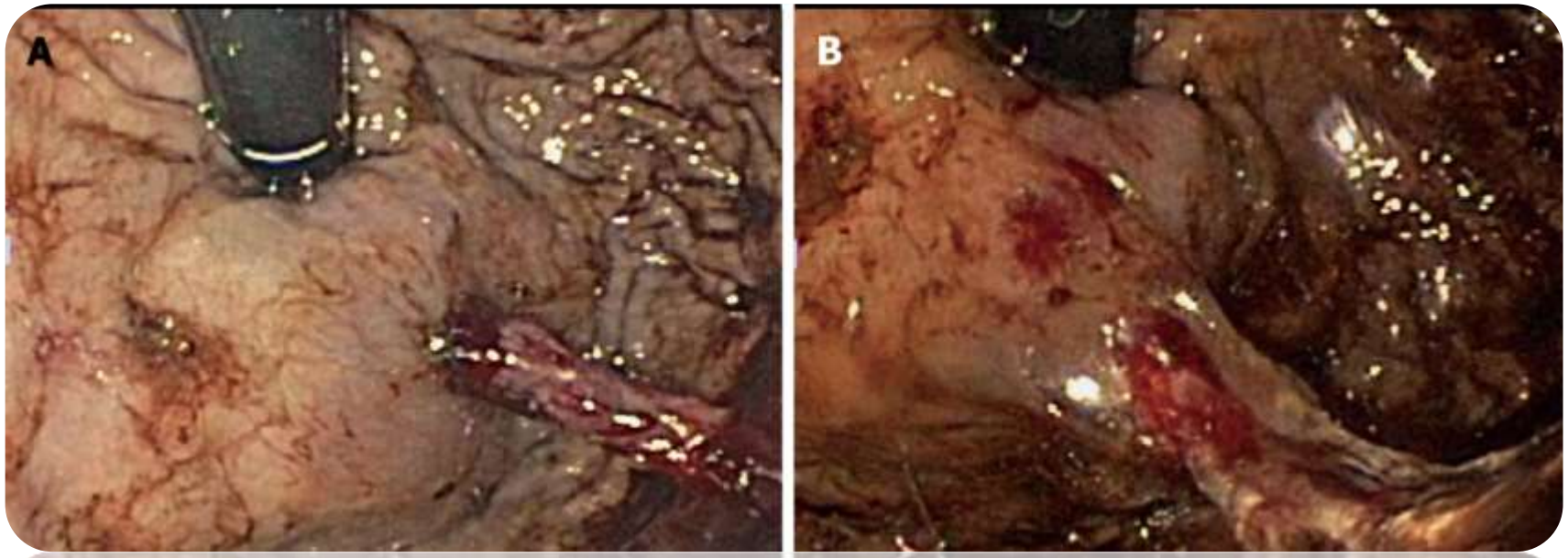


The hallmark of symptomatic AH is the abrupt onset **and/or rapid progression of jaundic**e, which may or may not be associated with fever, infection, weight loss, malnutrition, and an enlarged, tender liver.

In severe cases, AH may induce **liver decompensatio**n **with ascites, encephalopathy, or gastrointestinal bleeding**.

Patients with severe AH are prone to develop **bacterial infe**ction and acute **renal failure** due **to type 1 hepatorenal syndrome**

Acute alcoholic hepatitis



Alcoholic hepatitis

Prognosis (1)

Critically ill patients with alcoholic hepatitis have short-term (30 day) mortality rates >50%.

- Severe alcoholic hepatitis is heralded by coagulopathy (prothrombin time > 5 s), anemia, serum albumin concentrations >2.5 gr/dl serum bilirubin levels > 8 mg/dL, renal failure, and ascites.
- **A discriminant function** calculated as 4.6 x [prothrombin time control (seconds)] + serum bilirubin (mg/dL) **can identify patients with a poor** prognosis (**discriminant function > 32).**

Alcoholic hepatitis

Prognosis (2)

Critically ill patients with alcoholic hepatitis have short-term (30 day) mortality rates >50%.

- **The presence of ascites, variceal hemorrhage, severe encephalopathy or hepatorenal syndrome predicts a dismal prognosis**.
- The pathologic stage of the injury can be helpful in predicting prognosis. Liver biopsy should be performed whenever possible to confirm the diagnosis, to establish potential reversibility of the liver disease, and to guide the therapeutic decisions.

Alcoholic hepatitis

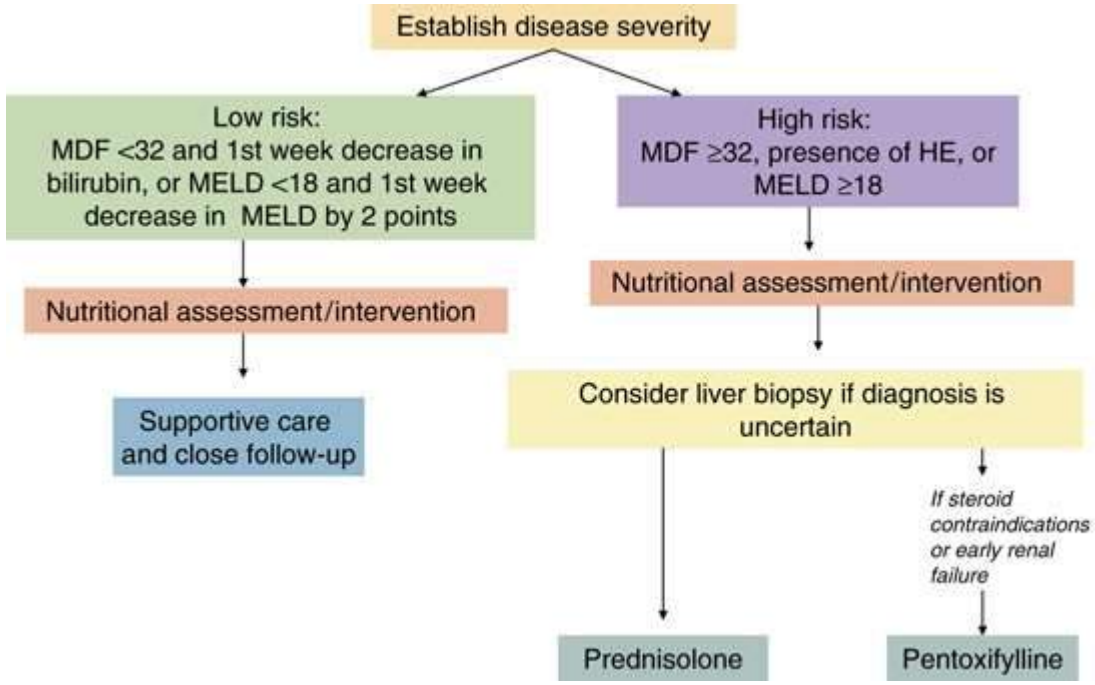
Predicting the evolution

Maddrey Discriminant Function

Laboratory Values Involved
1. Serum total bilirubin
2. Prothrombin time
3. Control prothrombin time

DF = (4.6 x [prothrombin time (sec) -control prothrombin time (sec)]) + (serum bilirubin)

	Non-severe Disease	Severe Disease
MDF score	< 32	> 32
Short-term mortality	10 %	30–60%
Corticosteroids?	No	Yes



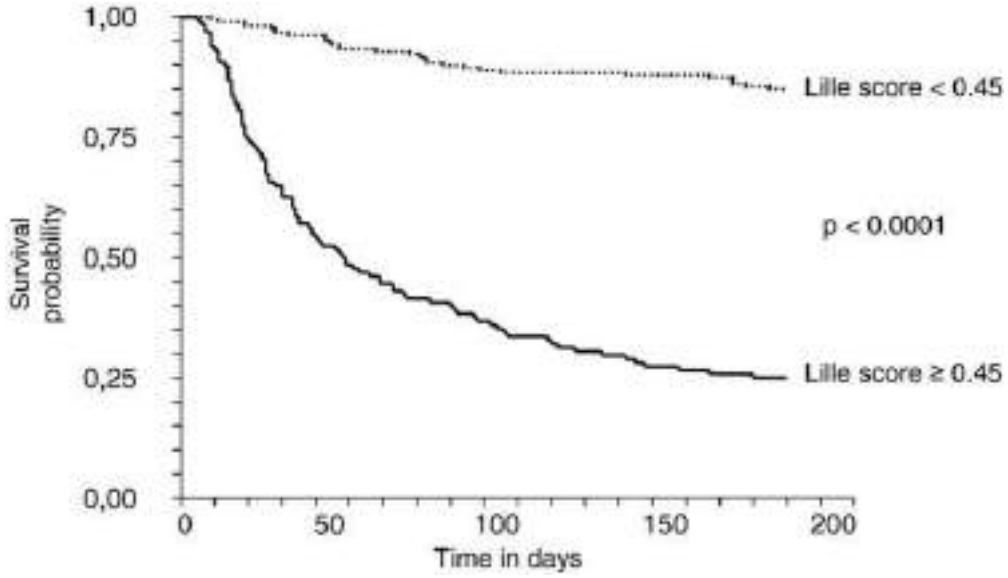
Alcoholic hepatitis

Lille model

- **Day 0: presence of encephalopaty + mDF (PT-PT control) + bilirubin**

- **Day 7: Bilirubin**

A value >0.5 predict 80% mortality whitin 6 months



Alcoholic liver disease

Treatment (1)

Regardless of the severity, **abstinence is the cornerstone of therapy and early management of alcohol abuse or dependence is warranted in all patients with ASH.**

Malnutrition is frequent and nutrition status should be evaluated.

Considering the potential risk of **Wernicke's encephalopathy,** supplementation with B-complex vitamins is recommended. Independent from hepatic encephalopathy, a daily protein intake of 1.5 g/kg of body weight should be ensured.

Liposoluble vitamins (A,D,E K) deficiency should be compensated.

Alcoholic liver disease

Treatment (2)

Patients with symptomatic forms of ASH often develop **acute renal failure which negatively impacts survival.**

The most frequent causes of acute renal failure are Type 1 hepatorenal syndrome.

Severe forms of ASH should be considered as a risk factor of radiocontrast-induced nephropathy.

Measures aimed at preventing the development of renal failure are recommended. They **include volume expansion** if needed and early treatment of hepatorenal syndrome.

Infections are frequent and difficult to diagnose in these patients since SIRS criteria is common at admission and could reflect either the inflammatory state associated with the ASH episode or an ongoing bacterial infection.

Alcoholic hepatitis

Treatment (3)

Patients with severe alcoholic hepatitis, **40 mg/d, or prednisolone,** for 4 weeks followed by a steroid taper. Exclusion criteria included active gastrointestinal bleeding, sepsis, renal failure, or pancreatitis.

Women with encephalopathy from severe alcoholic hepatitis may be particularly good candidates for glucocorticoids.

TNF inhibition as an alternative to glucocorticoids for severe alcoholic hepatitis. The nonspecific **TNFα inhibitor and pentoxifylline,** recently demonstrated improved survival in the therapy of severe alcoholic hepatitis

Alcoholic hepatitis

Treatment (4)

Most studies indicate that only a limited proportion of patients with severe forms of ASH benefit from corticosteroids.

Thus, early identification of non-responders to corticosteroids is important to define stopping rules and limit unnecessary exposure.

For example, after 7 days on corticosteroids, **a Lille score above 0.45 predicts poo**r response.

In poor responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).

In poor responders, an early switch to pentoxifylline or the use of a molecular adsorbent recirculating system (MARS) appears not to modify the outcome.

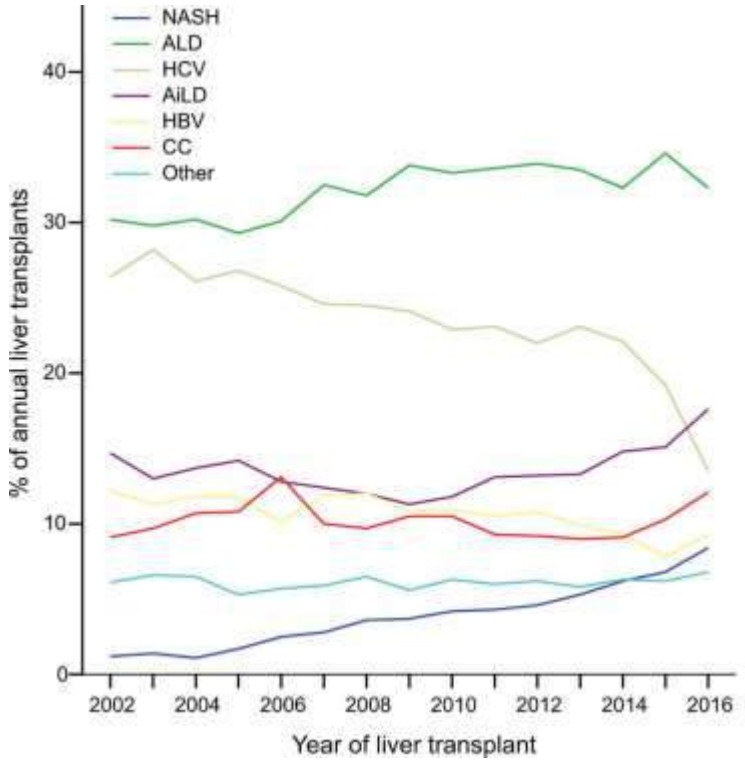
In these patients, early liver transplantation may be considered after a careful selection process.

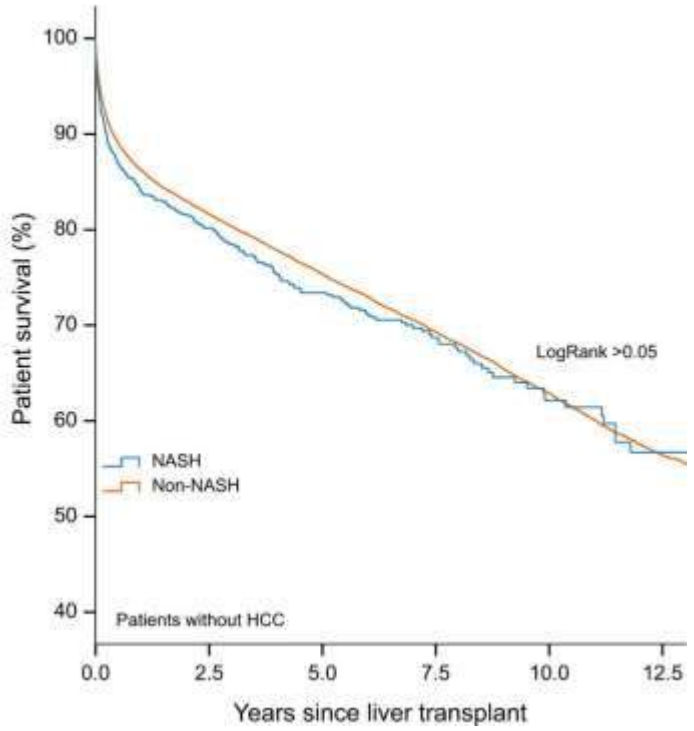
Alcoholic hepatitis

Treatment (5)

Liver transplant (1)

- The idea that alcoholism is self-inflicted must be reconciled with the strong evidence supporting genetic and environmental influences on alcohol dependence diagnosed by the DSM-IV diagnostic system.
- Graft and patient survival rates among alcoholics after **LT are similar** to those seen after transplantation for other aetiologies of liver disease.
- A significant increase in the proportion of patients transplanted for alcoholic liver disease was observed between the periods 1988–1995 and 1996–2005 in Europe

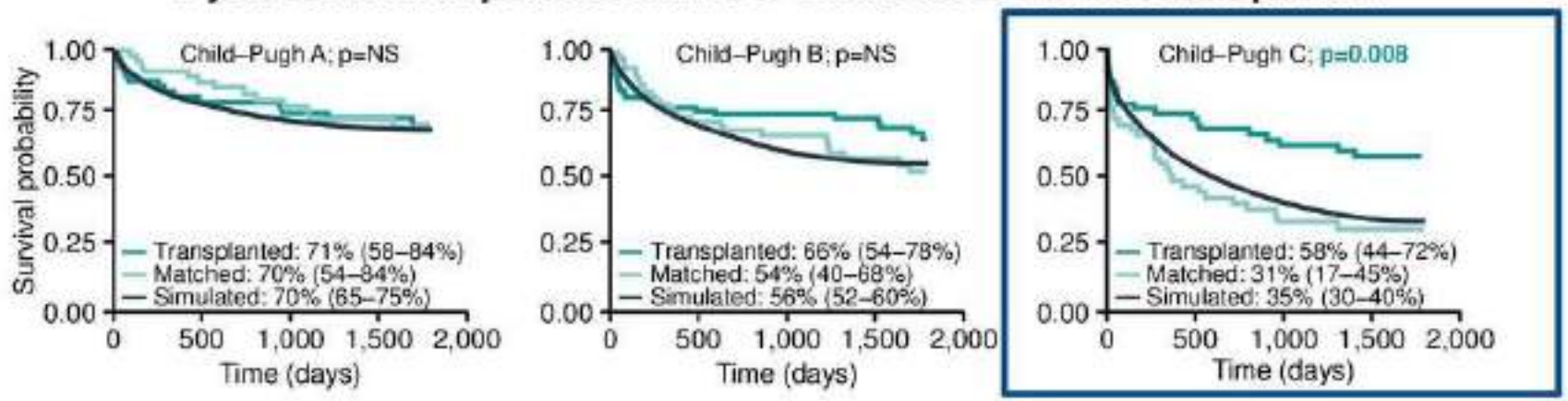




Alcoholic hepatitis

- Survival benefit related to LT is restricted to patients with **advanced** decompensation

5-year survival in patients with ALD cirrhosis: LT vs. non-transplanted[1]



- MELD accurately estimates the survival benefit following LT
  - Generally recommended to prioritize organ allocation
- Clinical manifestations of liver decompensation are not independent predictors of survival over and above MELD
  - Onset in an abstinent patient should prompt consideration of referral to a transplant centre
- Increasing evidence of the benefit of early LT in for patients with severe AH not responding to medical therapy
  - Selection criteria for such patients need to be more clearly defined

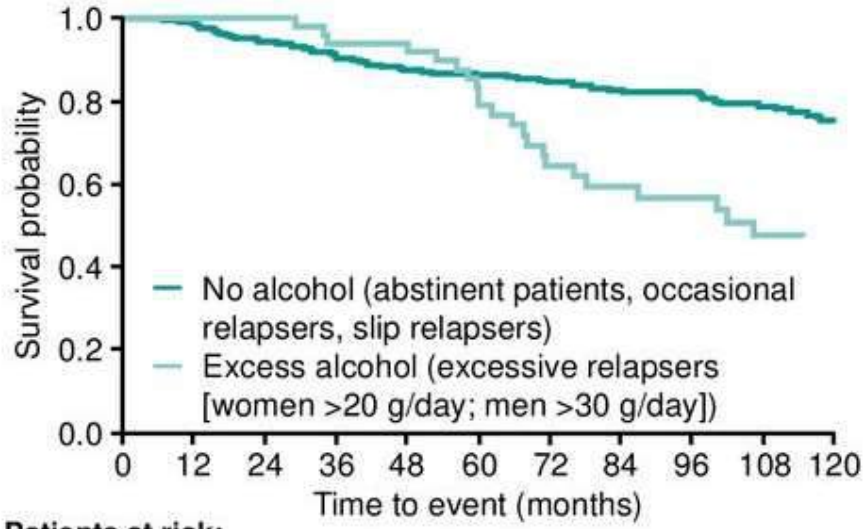
1. Poynard T, et al. J Hepatol 1999;30:1130–7;
EASL CPG ALD. J Hepatol 2018;69:154–81

EASL
The Home of Hepatology

Alcoholic liver disease

- Excessive alcohol consumption has a negative impact on long-term post-LT survival[1,2]
- Recipients with ALD are more likely to drink excessively[3]
- Multidisciplinary support pre- and post-LT has been shown to help prevent recidivism[4]

Comparison of Kaplan–Meier survival curves between excessive alcohol relapsers and other patients[1]



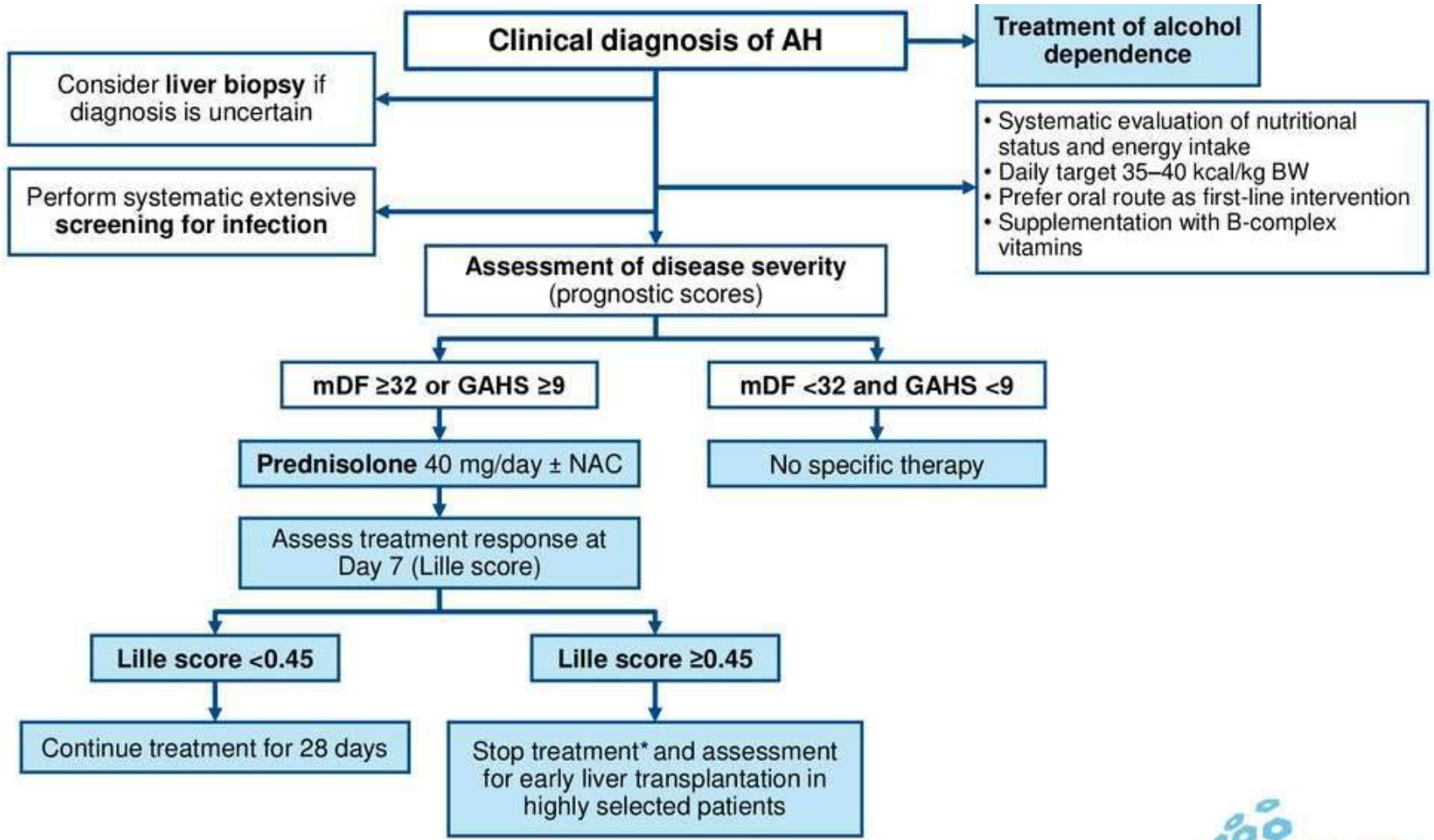
Patients at risk:

No alcohol	368	345	293	102
Excess alcohol	56	56	49	11

1. Faure S, et al. J Hepatol 2012;57:306–12; 2. Pfitzmann R, et al. Liver Transpl 2007;13:197–205;
3. Bravata DM, et al. Liver Transpl 2001;7:191–203; 4. Addolorato G, et al. Alcohol Clin Exp Res 2013;37:1601–8;
EASL CPG ALD. J Hepatol 2018;69:154–81

EASL™ The Home of Hepatology

Alcoholic hepatitis



*Particularly in null responders (Lille score ≥0.56).
EASL CPG ALD. J Hepatol 2018;69:154–81

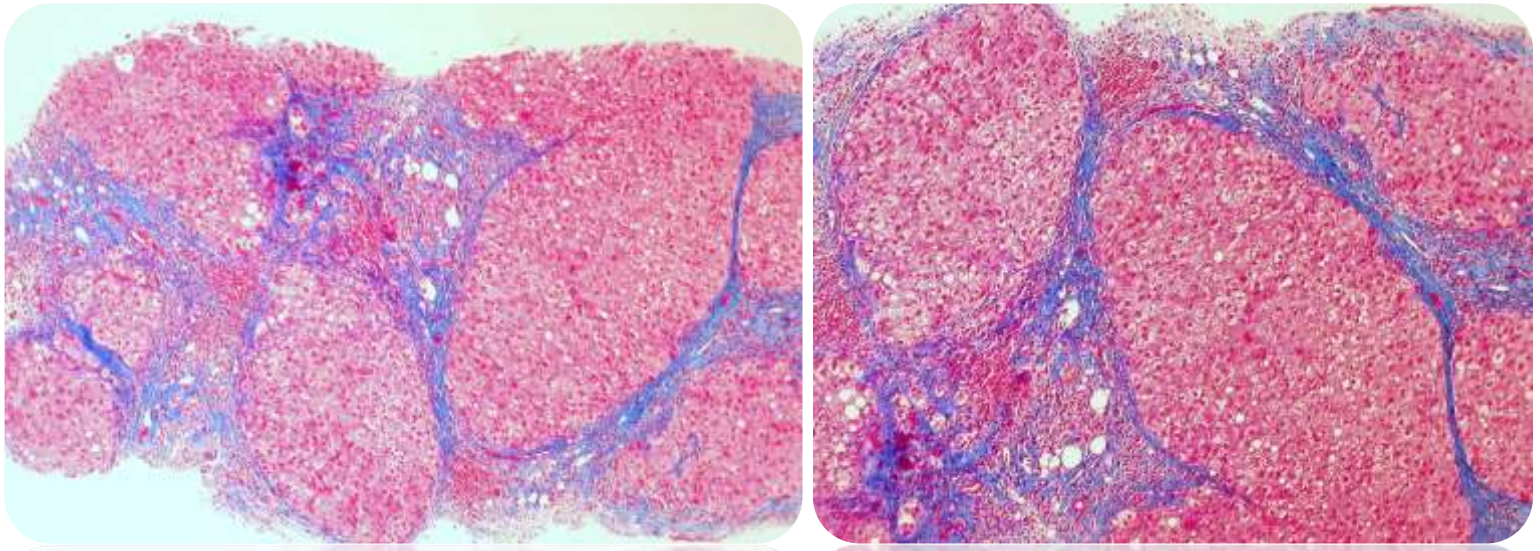
EASL
The Home of Hepatology

Alcoholic liver cirrhosis

- Excessive chronic alcohol use can cause several different types of chronic liver disease, including **alcoholic fatty liver**, **alcoholic hepatitis** and **alcoholic cirrhosis.**
- Furthermore, use of excessive alcohol can **contributes** to liver damage in patients with other liver diseases, such as hepatitis C, hemochromatosis, and fatty liver disease related to metabolic syndrome.

Alcoholic liver cirrhosis

- **Chronic alcohol use can produce fibrosis** in the absence of accompanying inflammation and/or necrosis.
- Fibrosis can be centrilobular, pericellular, or periportal.



Alcoholic liver cirrhosis

- When fibrosis reaches a certain degree, there is disruption of the normal liver architecture and **replacement of liver cells by regenerative nodules**. In alcoholic cirrhosis, the nodules are usually **<3 mm in diameter**; this form of cirrhosis is referred to as **micronodular**.
- With cessation of alcohol use, larger nodules may form, resulting in a **mixed micronodular and macronodular cirrhosis**